HETEROARYLS AND USES THEREOF

BACKGROUND OF THE INVENTION

[0001] Phosphatidylinositol 3-kinase (PI3K) is a family of lipid kinases that phosphorylate phosphatidylinositol at the 3' position of the inositol ring. PI3K is comprised of several classes of genes, including Class IA, IB, II and III and some of these classes contain several isoforms (reviewed in Engelman et al., Nature Review Genetics 7:606-619 (2006)). Adding to the complexity of this family is the fact that PI3Ks function as heterodimers, comprising a catalytic domain and a regulatory domain. The PI3K family is structurally related to a larger group of lipid and serine/threonine protein kinases known as the phosphatidylinositol 3-kinase like kinases (PIKKs), which also includes DNA-PK, ATM, ATR, mTOR, TRRAP and SMG1.

[0002] PI3K is activated downstream of various mitogenic signals mediated through receptor tyrosine kinases, and subsequently stimulates a variety of biological outcomes; including increased cell survival, cell cycle progression, cell growth, cell metabolism, cell migration and angiogenesis (reviewed in Cantley, Science 296:1655-57 (2002); Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005); Engelman et al., Nature Review Genetics 7:606-619 (2006)). Thus, PI3K hyper-activation is associated with a number of hyper-proliferative, inflammatory, or cardiovascular disorders; including cancer, inflammation, and cardiovascular disease.

[0003] There are a number of genetic aberrations that lead to constitutive PI3K signaling; including activating mutations in PI3K itself (Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005); reviewed in Bader et al., Nature Reviews Cancer 5:921-9 (2005)); RAS (reviewed in Downward Nature Reviews Cancer 3:11-22 (2003)) and upstream receptor tyrosine kinases (reviewed in Zwick et al., Trends in Molecular Medicine 8:17-23 (2002)) as well as inactivating mutations in the tumor suppressor PTEN (reviewed in Cully et al., Nature Reviews Cancer 6:184-92 (2006)). Mutations in each of these gene classes have proven to be oncogenic and are commonly found in a variety of cancers.

[0004] The molecules defined within this invention inhibit the activity of PI3K, and therefore may be useful for the treatment of proliferative, inflammatory, or cardiovascular disorders. Cases where PI3K pathway mutations have been linked to proliferative disorders where the molecules defined within this invention may have a therapeutic benefit include benign and malignant tumors and cancers from diverse lineage, including but not limited to those derived from colon (Samuels et al., Science 304:554 (2004); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), liver (reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), intestine (reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), stomach (Samuels et al., Science 304:554 (2004); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), esophagus (Phillips et al., International

Journal of Cancer 118:2644-6 (2006)); pancreas (reviewed in Downward Nature Reviews Cancer 3:11-22 (2003)); skin (reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), prostate (reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), lung (Samuels et al., Science 304:554 (2004); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), breast (Samuels et al., Science 304:554 (2004); Isakoff et al., Can Res 65:10992-1000 (2005); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), endometrium (Oda et al., Can Res 65:10669-73 (2005); reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), cervix (reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)); ovary (Shayesteh et al., Nature Genetics 21:99-102 (1999); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), testes (Moul et al., Genes Chromosomes Cancer 5:109-18 (1992); Di Vizio et al., Oncogene 24:1882-94 (2005)), hematological cells (reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006); Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), pancreas (reviewed in Downward Nature Reviews Cancer 3:11-22 (2003)), thyroid (reviewed in Downward Nature Reviews Cancer 3:11-22 (2003); reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)); brain (Samuels et al., Science 304:554 (2004); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), bladder (Lopez-Knowles et al., Cancer Research 66:7401-7404 (2006); Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)); kidney (reviewed in Downward Nature Reviews Cancer 3:11-22 (2003)) and Head and Neck (reviewed in Engelman et al., Nature Reviews Genetics 7:606-619 (2006)).

[0005] Other classes of disorders with aberrant PI3K pathway signaling where the molecules defined within this invention may have a therapeutic benefit include inflammatory and cardiovascular diseases, including but not limited to allergies/anaphylaxis (reviewed in Rommel et al., Nature Reviews Immunology 7:191-201 (2007)), acute and chronic inflammation (reviewed in Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006); reviewed in Rommel et al., Nature Reviews Immunology 7:191-201 (2007)), rheumatoid arthritis (reviewed in Rommel et al., Nature Reviews Immunology 7:191-201 (2007)); autoimmunity disorders (reviewed in Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006)), thrombosis (Jackson et al., Nature Medicine 11:507-14 (2005); reviewed in Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006)), hypertension (reviewed in Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006)), cardiac hypertrophy (reviewed in Proud et al., Cardiovascular Research 63:403-13 (2004)), and heart failure (reviewed in Mocanu et al., British Journal of Pharmacology 150:833-8 (2007)).

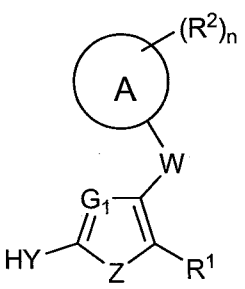
[0006] Vacuolar Protein Sorting 34 (VPS34) is the sole Class III PI3K family member. VPS34 functions in the formation and trafficking of multiple intracellular vesicles, including vacuoles, endosomes, multivessicular bodies, lysosomes and autophagosomes (reviewed in Backer Biochem J

2008; Yan and Backer Biochem J 2007). VPS34 carries out these activities by phosphorylating PtdIns forming PtdIns3P, resulting in the recruitment and localization of a variety of FYVE and PX domain containing effector proteins that facilitate vesicular formation, elongation and movement. At a cellular level, inhibition of VPS34 results in defects in protein sorting and autophagy. Broadly defined, autophagy is a regulated process whereby cells catabolize subcellular components targeted for degradation by enclosing them in double-membrane vesicles which then fuse with lysosomes. Autophagy has been best characterized as occurring during times of nutrient deprivation, but also plays a role in normal cellular and tissue homeostasis and functions, including the development of multiple tissue types, the immune response, clearance of neuronal aggregates and tumor suppression. In addition to functioning in vesicle formation and movement, VPS34 may also participate in several signal transduction pathways (reviewed in Backer Biochem J 2008). Given that VPS34 plays an important role in many critical cellular processes including autophagy, inhibitors of VPS34 may have therapeutic application in a number of diseases, including but not limited to cancer, muscular disorders, neurodegeneration, inflammatory disease, infectious disease and other age related illnesses (reviewed in Shintani and Klionshy Science 2004; Kondo et al Nat Rev Cancer 2005; Delgato et al Immunol Rev 2009).

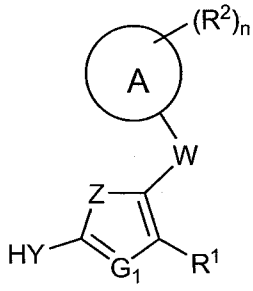
[0007] Clearly, it would be beneficial to provide novel PI3K inhibitors that possess good therapeutic properties, especially for the treatment of proliferative, inflammatory, or cardiovascular disorders.

[0008] *1. General Description of Compounds of the Invention:*

[0009] This invention provides compounds that are inhibitors of PI3K, and accordingly are useful for the treatment of proliferative, inflammatory, or cardiovascular disorders. In one embodiment, the compounds of this invention are represented by formula **IA-a** or **IB-a**:



IA-a

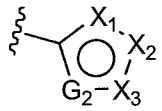


IB-a

or a pharmaceutically acceptable salt thereof, wherein:

Z is S or Se;

R^1 is CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N\text{-}NH_2)NH_2$, $-C(=N)N(R^3)_2$, wherein:

CY is  ; wherein:

G_2 is –N= , =N–, or $–N(R^{3'})$ –, wherein:

each occurrence of R^3 and $R^{3'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_1, X_2, and X_3, are each independently N, $NR^{3'}$, O, S, or CR^4, provided that only one of X_1, X_2, or X_3 may be O, S, or $NR^{3'}$;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $–Z_3\text{-}R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})$-, -S-, -S(O)-, $-S(O)_2$-, -C(O)-, $-CO_2$-, $-C(O)NR^{4a}$-, $-N(R^{4a})C(O)$-, $-N(R^{4a})CO_2$-, $-S(O)_2NR^{4a}$-, $-N(R^{4a})S(O)_2$-, $-OC(O)N(R^{4a})$-, $-N(R^{4a})C(O)NR^{4a}$-, $-N(R^{4a})S(O)_2N(R^{4a})$-, or -OC(O)-;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein two adjacent occurrences of $R^{3'}$ or R^4, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $–R^{12a}$, $-T_2\text{-}R^{12d}$, or $–V_2\text{-}T_2\text{-}R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$,

$-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl

having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, -$C(O)R^{7a}$, -$C(O)OR^{7a}$, $S(O)R^{7a}$, or -$S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

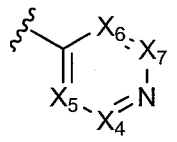
G_1 is N or -CR^8, wherein R^8 is H, –CN, halogen, –Z_2-R^9, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, -$N(R^{8a})$-, -S-, -$S(O)$-, $S(O)_2$-, -$C(O)$-, -CO_2-, -$C(O)NR^{8a}$-, -$N(R^{8a})C(O)$-, -$N(R^{8a})CO_2$-, -$S(O)_2NR^{8a}$-, -$N(R^{8a})S(O)_2$-, -$OC(O)N(R^{8a})$-, -$N(R^{8a})C(O)NR^{8a}$-, -$N(R^{8a})S(O)_2N(R^{8a})$-, or -$OC(O)$-;

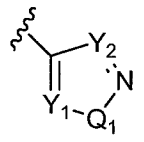
R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

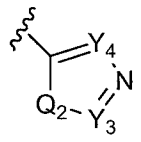
HY is an optionally substituted group selected from:



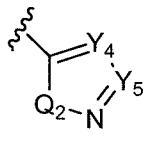
A ,



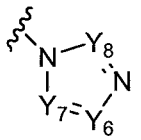
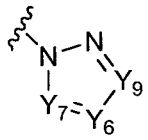
B ,



C ,



D

E , or **F** ;

wherein each occurrence of X_4, X_5, X_6, and X_7 is independently $-CR^{10}$ or N, provided no more than two occurrences of X_4, X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $-NR^5$;

each occurrence of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, and Y_9 is independently $-CR^{10}$ or N, provided no more than two occurrences of Y_6, Y_7, Y_8, and Y_9 are N;

or wherein two adjacent occurrences of X_4 and X_5, X_6 and X_7, Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein R^{10} is $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, or $-V_1-T_1-R^{10b}$ wherein:

V_1 is $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, or $-SO_2NR^{11}-$;

each occurrence of R^{10a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ or wherein T_1 forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

each occurrence of R^{10b} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$,

$-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{10c} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

R^{10a} and R^{10c} taken together with a nitrogen atom to which they are bound form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{11} is independently hydrogen, $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{11a} is independently hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

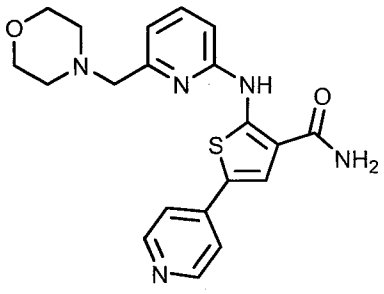
each occurrence of R^5 is independently hydrogen, $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{5a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

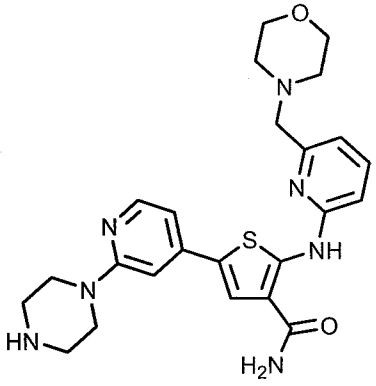
wherein each occurrence of R^{5b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R^{5b} taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

provided that:

a) for compounds of formula IB-a compounds are other than:

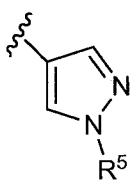


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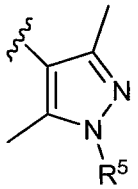


; and

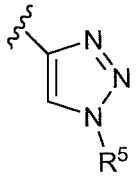
when G^1 is CR^8, R^1 is $CONH_2$, and W is NH, then HY is other than



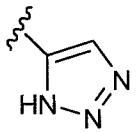
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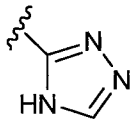
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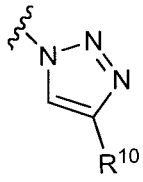
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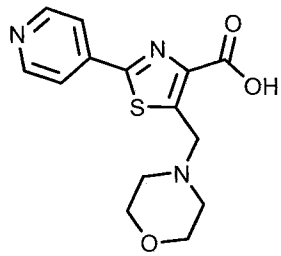
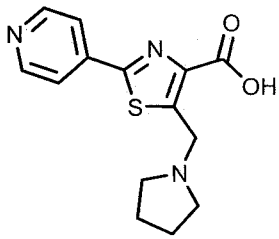
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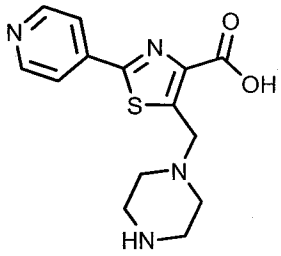
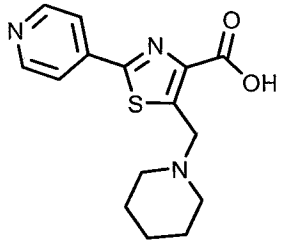
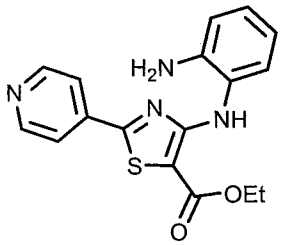
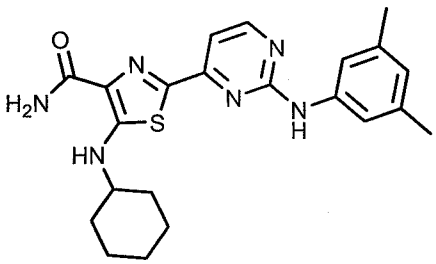
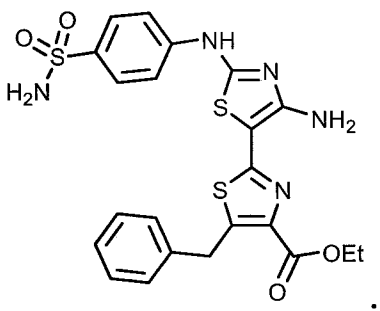
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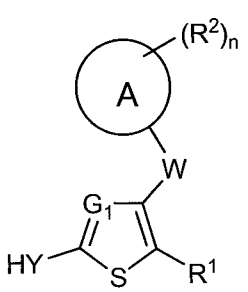
, or ; and

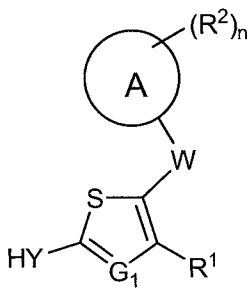
b) the compound is other than:

[0010] In another embodiment, the compounds of this invention are represented by formula **IA** or **IB**:



IA

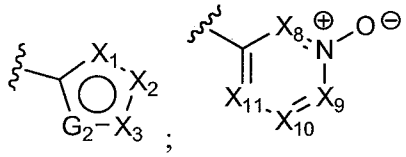


IB

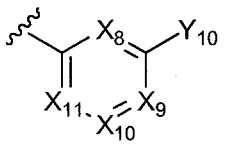
or a pharmaceutically acceptable salt thereof, wherein:

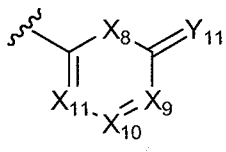
R^1 is CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N\text{-}NH_2)NH_2$, $-C(=N)N(R^3)_2$, wherein:

CY is an optionally substituted group selected from:



;

; 

; and 

;

Q **R** **S** **T**

wherein:

G_2 is –N= , =N–, or $-N(R^{3'})-$, wherein:

each occurrence of R^3 and $R^{3'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_1, X_2, and X_3, are each independently N, $NR^{3'}$, O, S, or CR^4, provided that only one of X_1, X_2, or X_3 may be O, S, or $NR^{3'}$;

X_8, X_9, X_{10}, and X_{11} are each independently N, or CR^4, provided no more than two occurrences of X_8, X_9, X_{10}, and X_{11} are N;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $-Z_3\text{-}R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})$-, -S-, -S(O)-, $-S(O)_2$-, -C(O)-, $-CO_2$-, $-C(O)NR^{4a}$-, $-N(R^{4a})C(O)$-, $-N(R^{4a})CO_2$-, $-S(O)_2NR^{4a}$-, $-N(R^{4a})S(O)_2$-, $-OC(O)N(R^{4a})$-, $-N(R^{4a})C(O)NR^{4a}$-, $-N(R^{4a})S(O)_2N(R^{4a})$-, or -OC(O)-;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein two adjacent occurrences of $R^{3'}$ or R^4, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Y_{10} is $-OR^{4'}$ or $-N(R^{4'})_2$;

Y_{11} is O or N-$R^{4'}$;

each occurrence of $R^{4'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, -OC(O)-, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by -$N(R^{13})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -$C(O)N(R^{13})$-, -$S(O)_2N(R^{13})$-, -$OC(O)N(R^{13})$-, -$N(R^{13})C(O)$-, -$N(R^{13})SO_2$-, -$N(R^{13})C(O)O$-, -$N(R^{13})C(O)N(R^{13})$-, -$N(R^{13})S(O)_2N(R^{13})$-, -OC(O)-, or -$C(O)N(R^{13})$-O- or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from –$C(R^7)_2$-, –$C(=C(R^7)_2)$-, -$C(R^7)_2O$-, -$C(R^7)_2NR^{7a}$-, –O-, -$N(R^{7b})$-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -$C(O)NR^{7a}$-, or -$N(R^{7a})C(O)$-, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, -$C(O)R^{7a}$, -$C(O)OR^{7a}$, $S(O)R^{7a}$, or -$S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

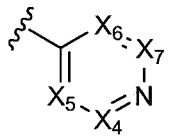
G_1 is N or -CR^8, wherein R^8 is H, –CN, halogen, –Z_2-R^9, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, -$N(R^{8a})$-, -S-, -S(O)-, $S(O)_2$-, -C(O)-, -CO_2-, -$C(O)NR^{8a}$-, -$N(R^{8a})C(O)$-, -$N(R^{8a})CO_2$-, -$S(O)_2NR^{8a}$-, -$N(R^{8a})S(O)_2$-, -$OC(O)N(R^{8a})$-, -$N(R^{8a})C(O)NR^{8a}$-, -$N(R^{8a})S(O)_2N(R^{8a})$-, or -OC(O)-;

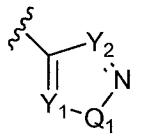
R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

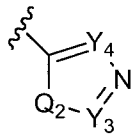
HY is an optionally substituted group selected from:



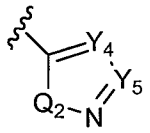
A ,



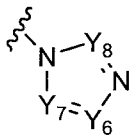
B ,



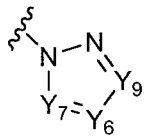
C ,



D



E ,



or **F** ;

wherein each occurrence of X_4, X_5, X_6, and X_7 is independently $-CR^{10}$ or N, provided no more than two occurrences of X_4, X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $-NR^5$;

each occurrence of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, and Y_9 is independently $-CR^{10}$ or N, provided no more than two occurrences of Y_6, Y_7, Y_8, and Y_9 are N;

or wherein two adjacent occurrences of X_4 and X_5, X_6 and X_7, Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein R^{10} is $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, or $-V_1-T_1-R^{10b}$ wherein:

V_1 is $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, or $-SO_2NR^{11}-$;

each occurrence of R^{10a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ or wherein T_1 forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

each occurrence of R^{10b} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{10c} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

R^{10a} and R^{10c} taken together with a nitrogen atom to which they are bound form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{11} is independently hydrogen, $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{11a} is independently hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

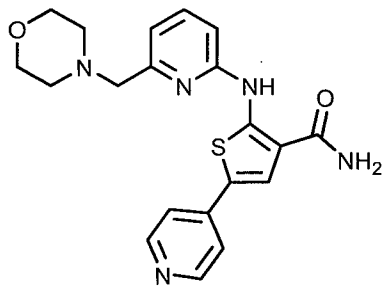
each occurrence of R^5 is independently hydrogen, $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{5a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

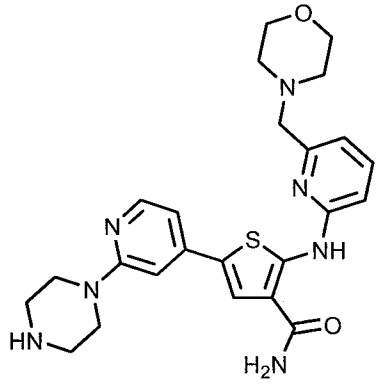
wherein each occurrence of R^{5b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R^{5b} taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

a) for compounds of formula IB compounds are other than:

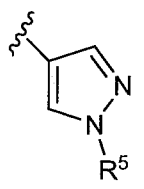
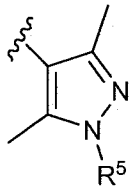
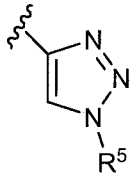
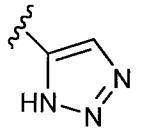
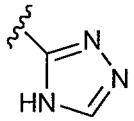
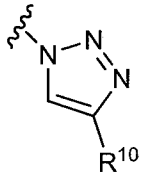


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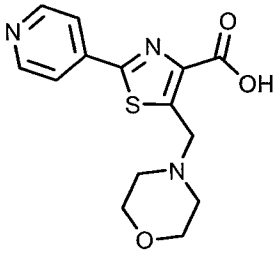
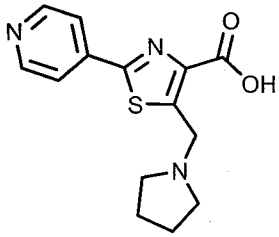
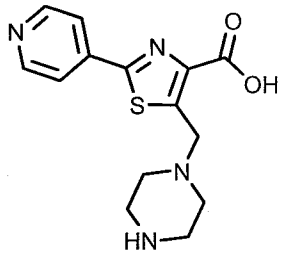
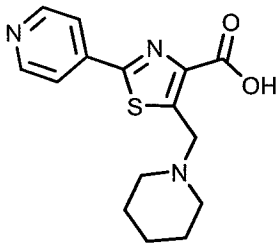
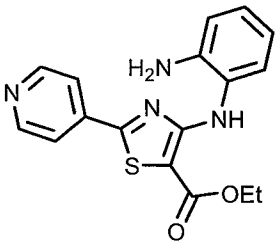
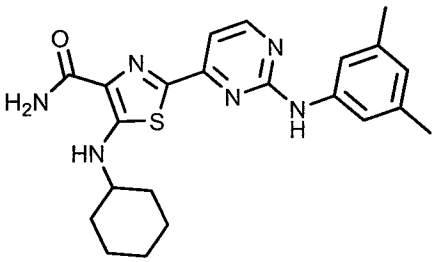
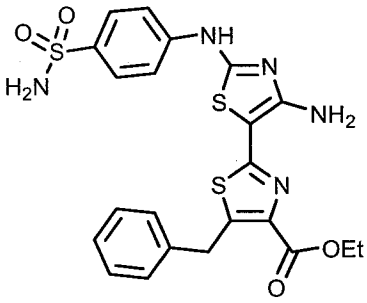


; and

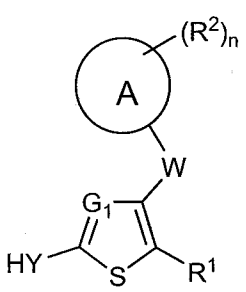
when G^1 is CR^8, R^1 is $CONH_2$, and W is NH, then HY is other than




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,
, or ; and

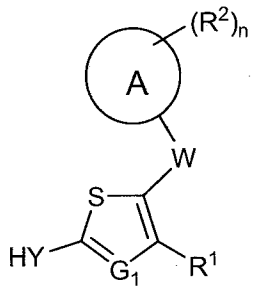
b) the compound is other than:





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[0011] In another aspect, the compounds of this invention are represented by formula **IA** or **IB**:



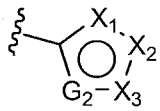
IA



IB

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N\text{-}NH_2)NH_2$, $-C(=N)N(R^3)_2$, wherein:

CY is  ; wherein:

G_2 is –N= , =N–, or $-N(R^{3'})-$, wherein:

each occurrence of R^3 and $R^{3'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_1, X_2, and X_3, are each independently N, $NR^{3'}$, O, S, or CR^4, provided that only one of X_1, X_2, or X_3 may be O, S, or $NR^{3'}$;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $-Z_3\text{-}R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$, $-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, or -OC(O)-;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein two adjacent occurrences of $R^{3'}$ or R^4, taken together with the atom to which they are bound, form an optionally substituted fused group selected from

5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, -OC(O)-, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted

by -N(R^{13})-, -O-, -S-, -S(O)-, -S($O)_2$-, -C(O)-, -C(O)O-, -C(O)N(R^{13})-, -S($O)_2$N(R^{13})-, -OC(O)N(R^{13})-, -N(R^{13})C(O)-, -N(R^{13})SO_2-, -N(R^{13})C(O)O-, -N(R^{13})C(O)N(R^{13})-, -N(R^{13})S($O)_2$N(R^{13})-, -OC(O)-, or -C(O)N(R^{13})-O- or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from –C($R^7)_2$-, –C(=C($R^7)_2$)-, -C($R^7)_2$O-, -C($R^7)_2$NR^{7a}-, –O-, -N(R^{7b})-, -S-, -S(O)-, -S($O)_2$-, -C(O)-, -C(O)NR^{7a}-, or -N(R^{7a})C(O)-, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -N($R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, -C(O)R^{7a}, -C(O)OR^{7a}, S(O)R^{7a}, or -S($O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N or -CR^8, wherein R^8 is H, –CN, halogen, –Z_2-R^9, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, -N(R^{8a})-, -S-, -S(O)-, S($O)_2$-, -C(O)-, -CO_2-, -C(O)NR^{8a}-, -N(R^{8a})C(O)-, -N(R^{8a})CO_2-, -S($O)_2$NR^{8a}-, -

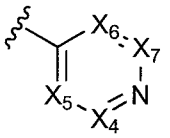
$N(R^{8a})S(O)_2$-,

-$OC(O)N(R^{8a})$-, -$N(R^{8a})C(O)NR^{8a}$-, -$N(R^{8a})S(O)_2N(R^{8a})$-, or -OC(O)-;

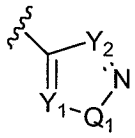
R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

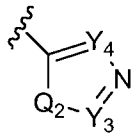
HY is an optionally substituted group selected from:



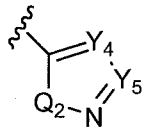
A ,



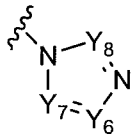
B,



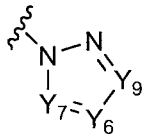
C,



D,



E, or



F;

wherein each occurrence of X_4, X_5, X_6, and X_7 is independently $-CR^{10}$ or N, provided no more than two occurrences of X_4, X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $-NR^5$;

each occurrence of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, and Y_9 is independently -CR^{10} or N, provided no more than two occurrences of Y_6, Y_7, Y_8, and Y_9 are N;

or wherein two adjacent occurrences of X_4 and X_5, X_6 and X_7, Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein R^{10} is $-R^{10b}$, $-V_1$-R^{10c}, -T_1-R^{10b}, or -V_1-T_1-R^{10b} wherein:

V_1 is $-NR^{11}$-, -NR^{11}-C(O)-, -NR^{11}-C(S)-, -NR^{11}-$C(NR^{11})$-, -$NR^{11}C(O)OR^{10a}$-, -$NR^{11}C(O)NR^{11}$-, -$NR^{11}C(O)SR^{10a}$-, -$NR^{11}C(S)OR^{10a}$-, -$NR^{11}C(S)NR^{11}$-, -$NR^{11}C(S)SR^{10a}$-, -$NR^{11}C(NR^{11})OR^{10a}$-, -$NR^{11}C(NR^{11})NR^{11}$-, -$NR^{11}S(O)_2$-, -$NR^{11}S(O)_2NR^{11}$-, -C(O)-, -$CO_2$-, -$C(O)NR^{11}$-, -$C(O)NR^{11}O$-, -$SO_2$-, or -$SO_2NR^{11}$-;

each occurrence of R^{10a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered

heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ or wherein T_1 forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

each occurrence of R^{10b} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{10c} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

R^{10a} and R^{10c} taken together with a nitrogen atom to which they are bound form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{11} is independently hydrogen, $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{11a} is independently hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5

heteroatoms independently selected from nitrogen, oxygen, or sulfur;

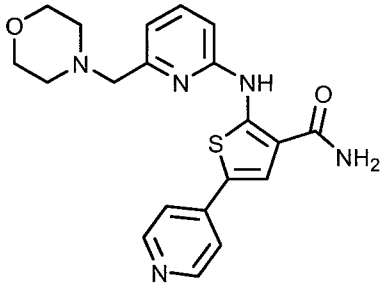
each occurrence of R^5 is independently hydrogen, $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{5a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

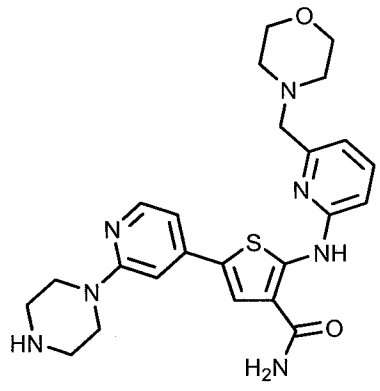
wherein each occurrence of R^{5b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R^{5b} taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

a) for compounds of formula IB compounds are other than:

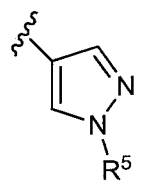
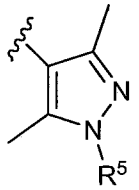
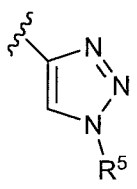
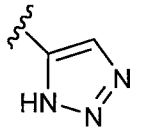
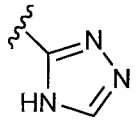
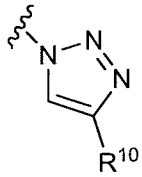


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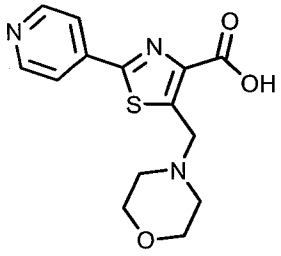
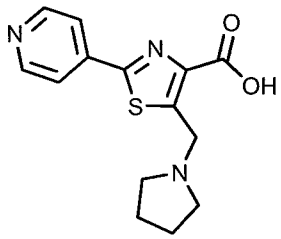
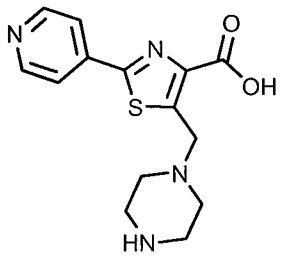
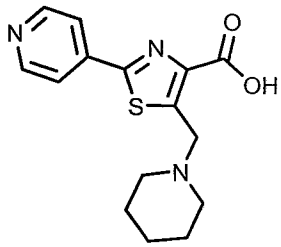
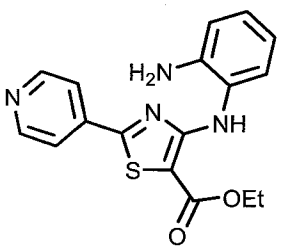
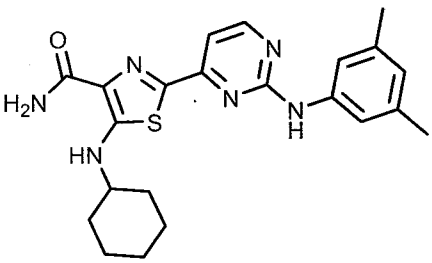
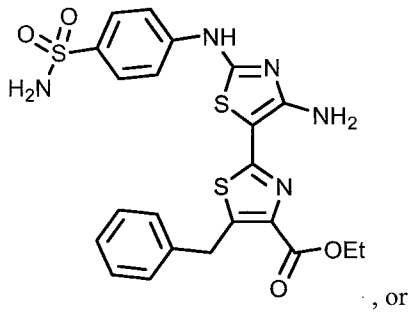
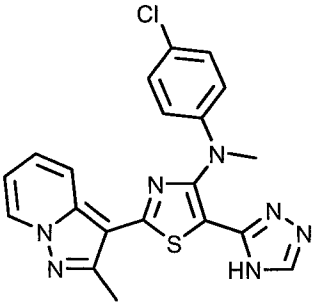


; and

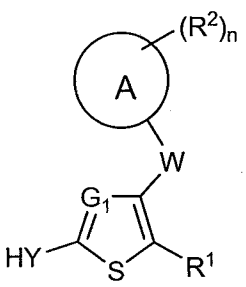
when G^1 is CR^8, R^1 is $CONH_2$, and W is NH, then HY is other than




,



, or ; and

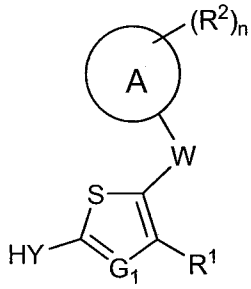
b) the compound is other than:








, or

.

[0012] In another aspect, the compounds of this invention are represented by formula **IA** or **IB**:



IA



IB

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N-NH_2)NH_2$, $-C(=N)N(R^3)_2$;

each occurrence of R^3 is independently hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or $-CN$;

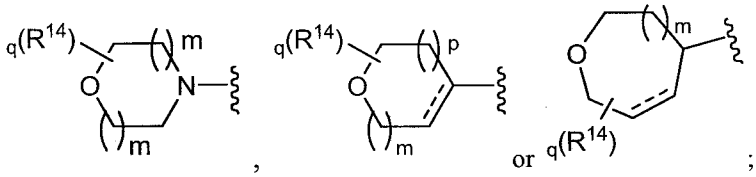
each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N; and

HY is ;

wherein each occurrence of R^{14} is independently–R^{14a} or -T_1-R^{14d}, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, -NO_2, -R^{14c}, -$N(R^{14b})_2$, -OR^{14b}, -SR^{14c}, -$S(O)_2R^{14c}$, -$C(O)R^{14b}$, -$C(O)OR^{14b}$, -$C(O)N(R^{14b})_2$, -$S(O)_2N(R^{14b})_2$, -$OC(O)N(R^{14b})_2$, -$N(R^{14e})C(O)R^{14b}$, -$N(R^{14e})SO_2R^{14c}$, -$N(R^{14e})C(O)OR^{14b}$, -$N(R^{14e})C(O)N(R^{14b})_2$, or –$N(R^{14e})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

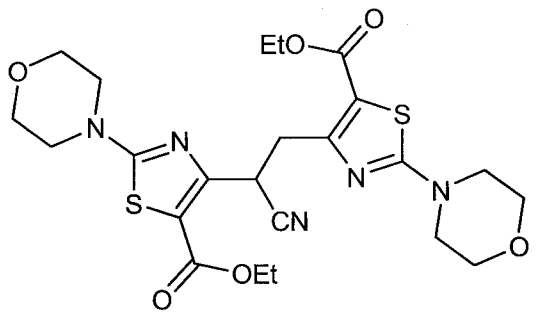
T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, or $-C(O)N(R^{14a})-O-$ or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

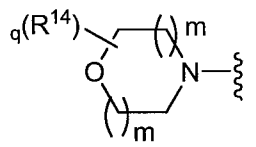
n is 0-6;

m is 1 or 2;

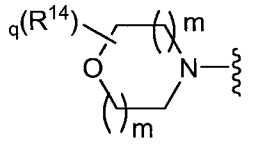
p is 0, 1, or 2;

provided that the compound is other than:



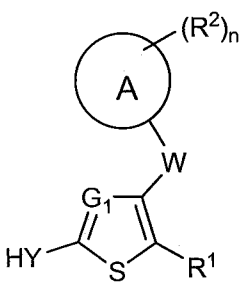


[0013] In some embodiments for compounds described directly above, HY is , wherein both occurrences of m are 1.

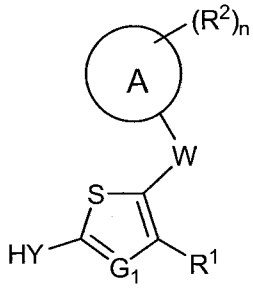


[0014] In other embodiments for compounds described directly above, HY is , wherein both occurrences of m are 1, and R^1 is COOH.

[0015] In yet another aspect, the compounds of this invention are represented by formula **IA** or **IB**:



IA

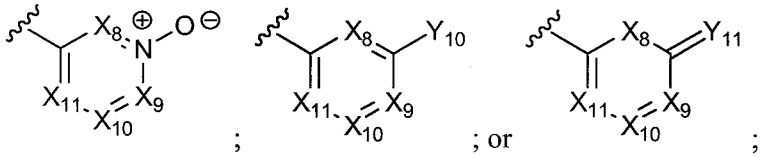


IB

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is CY, wherein:

CY is an optionally substituted group selected from:



R ; S ; or T ;

wherein:

each occurrence of R^3 is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_8, X_9, X_{10}, and X_{11} are each independently N, or CR^4, provided no more than two occurrences of X_8, X_9, X_{10}, and X_{11} are N;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $-Z_3-R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$, $-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, or -OC(O)-;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Y_{10} is $-OR^{4'}$ or $-N(R^{4'})_2$;

Y_{11} is O or $N-R^{4'}$;

each occurrence of $R^{4'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, -OC(O)-, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by -$N(R^{13})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -C(O)$N(R^{13})$-, -$S(O)_2N(R^{13})$-, -OC(O)$N(R^{13})$-, -$N(R^{13})$C(O)-, -$N(R^{13})SO_2$-, -$N(R^{13})$C(O)O-, -$N(R^{13})$C(O)$N(R^{13})$-, -$N(R^{13})S(O)_2N(R^{13})$-, -OC(O)-, or -C(O)$N(R^{13})$-O- or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from –$C(R^7)_2$-, –C(=$C(R^7)_2$)-, -$C(R^7)_2$O-, -$C(R^7)_2NR^{7a}$-, –O-, -$N(R^{7b})$-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)NR^{7a}-, or -$N(R^{7a})$C(O)-, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, -C(O)R^{7a}, -C(O)OR^{7a}, S(O)R^{7a}, or -$S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

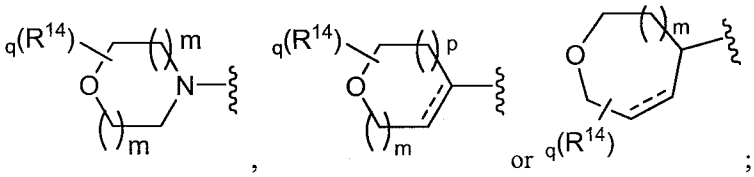
or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N or -CR^8, wherein R^8 is H, –CN, halogen, –Z_2-R^9, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, -$N(R^{8a})$-, -S-, -S(O)-, $S(O)_2$-, -C(O)-, -CO_2-, -C(O)NR^{8a}-, -$N(R^{8a})$C(O)-, -$N(R^{8a})CO_2$-, -$S(O)_2NR^{8a}$-, -$N(R^{8a})S(O)_2$-, -OC(O)$N(R^{8a})$-, -$N(R^{8a})$C(O)NR^{8a}-, -$N(R^{8a})S(O)_2N(R^{8a})$-, or -OC(O)-;

R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

HY is 

wherein each occurrence of R^{14} is independently–R^{14a} or -T_1-R^{14d}, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, -NO_2, -R^{14c}, -$N(R^{14b})_2$, -OR^{14b}, -SR^{14c}, -$S(O)_2R^{14c}$, -$C(O)R^{14b}$, -$C(O)OR^{14b}$, -$C(O)N(R^{14b})_2$, -$S(O)_2N(R^{14b})_2$, -$OC(O)N(R^{14b})_2$, -$N(R^{14e})C(O)R^{14b}$, -$N(R^{14e})SO_2R^{14c}$, -$N(R^{14e})C(O)OR^{14b}$, -$N(R^{14e})C(O)N(R^{14b})_2$, or –$N(R^{14e})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted

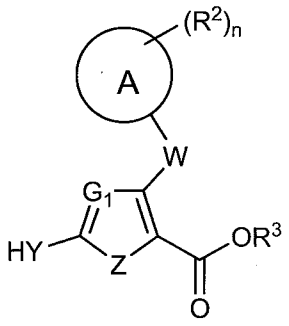
by $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, or $-C(O)N(R^{14a})-O-$ or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

n is 0-6;

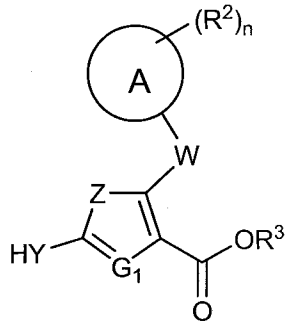
m is 1 or 2; and

p is 0, 1, or 2.

[0016] In still another embodiment of the invention, compounds of this invention are represented by formula **IA-i-a** or **IB-i-a**:



IA-i-a



IB-i-a

or a pharmaceutically acceptable salt thereof, wherein:

Z is S or Se;

R^3 is hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, or:

two adjacent R^2 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen, $-N(R^{7b})_2$, or an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, -OC(O)-, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, -OC(O)-, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

W is selected from a covalent bond, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, -O-, $-N(R^{7b})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -$N(R^{7b})_2$, -OR^{7c}, -SR^{7a}, or F;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, -$C(O)R^{7a}$, -$C(O)OR^{7a}$, $S(O)R^{7a}$, or -$S(O)_2R^{7a}$; or

each occurrence of R^{7c} is independently an optionally substituted C_{1-6}aliphatic or an optionally substituted 3-7 membered cycloalphatic; or

wherein any two occurrences of R^7, R^{7a}, R^{7b} , or R^{7c}, taken together with atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

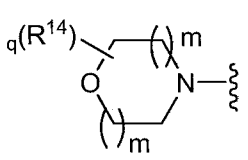
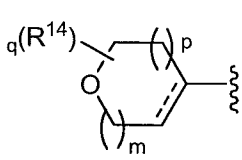
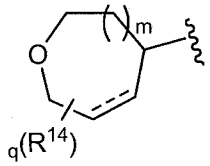
or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N or -CR^8, wherein R^8 is H, –CN, halogen, –Z_2-R^9, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, -$N(R^{8a})$-, -S-, -S(O)-, $S(O)_2$-, -C(O)-, -CO_2-, -$C(O)NR^{8a}$-, -$N(R^{8a})C(O)$-, -$N(R^{8a})CO_2$-, -$S(O)_2NR^{8a}$-, -$N(R^{8a})S(O)_2$-, -$OC(O)N(R^{8a})$-, -$N(R^{8a})C(O)NR^{8a}$-, -$N(R^{8a})S(O)_2N(R^{8a})$-, or -OC(O)-;

R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

HY is  ,  or  ;

$\overline{\text{------}}$ represents a single bond or a double bond;

wherein each occurrence of R^{14} is independently–R^{14a} or -T_1-R^{14d}, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, -NO_2, -R^{14c}, -$N(R^{14b})_2$, -OR^{14b}, -SR^{14c}, -$S(O)_2R^{14c}$, -$C(O)R^{14b}$, -$C(O)OR^{14b}$, -$C(O)N(R^{14b})_2$, -$S(O)_2N(R^{14b})_2$, -$OC(O)N(R^{14b})_2$, -$N(R^{14e})C(O)R^{14b}$, -$N(R^{14e})SO_2R^{14c}$, -$N(R^{14e})C(O)OR^{14b}$, -$N(R^{14e})C(O)N(R^{14b})_2$, or –$N(R^{14e})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

T_1 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by -$N(R^{14a})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -$C(O)N(R^{14a})$-, -$S(O)_2N(R^{14a})$-, -$OC(O)N(R^{14a})$-, -$N(R^{14a})C(O)$-, -$N(R^{14a})SO_2$-, -$N(R^{14a})C(O)O$-, -$NR^{14a}C(O)N(R^{14a})$-,

$-N(R^{14a})S(O)_2N(R^{14a})-$, -OC(O)-, or $-C(O)N(R^{14a})-O-$ or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

n is 0-6;

q is 0-4;

m is 1 or 2; and

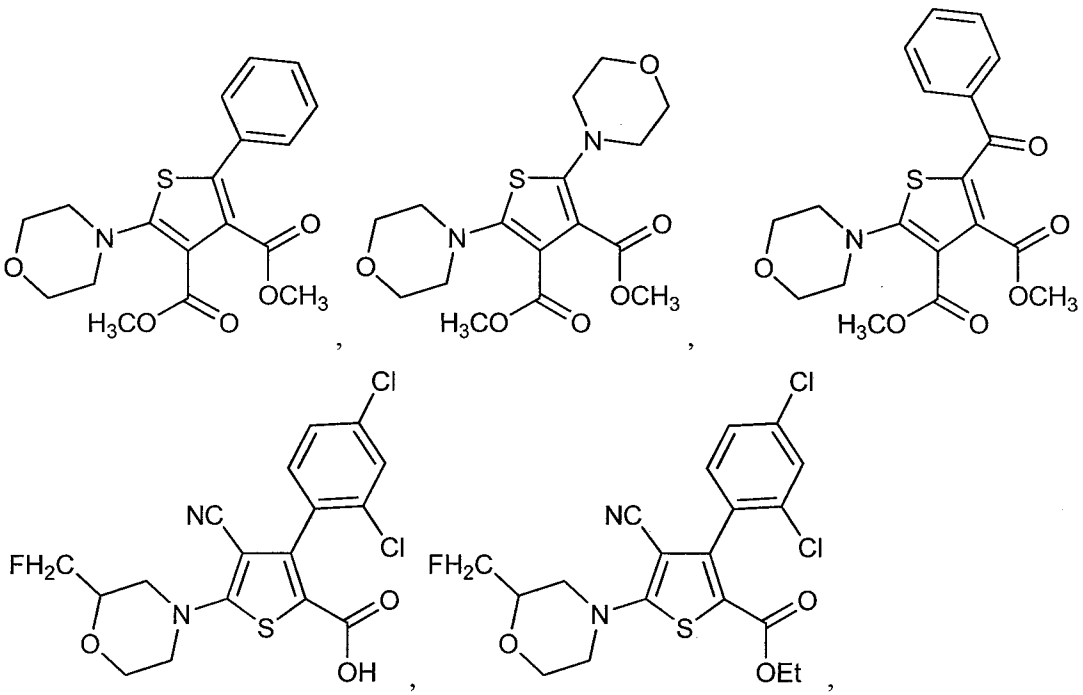
p is 0, 1, or 2;

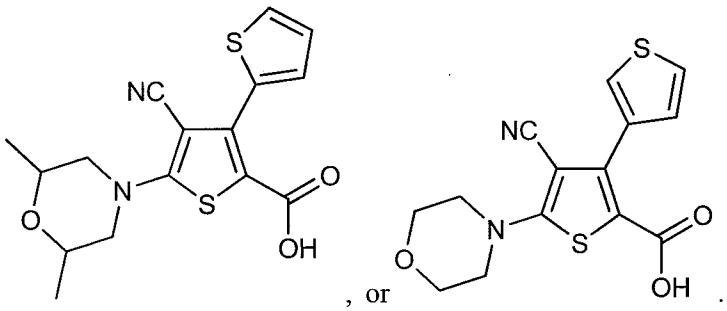
provided that:

a) when G_1 is C-CN, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

b) when G_1 is N, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

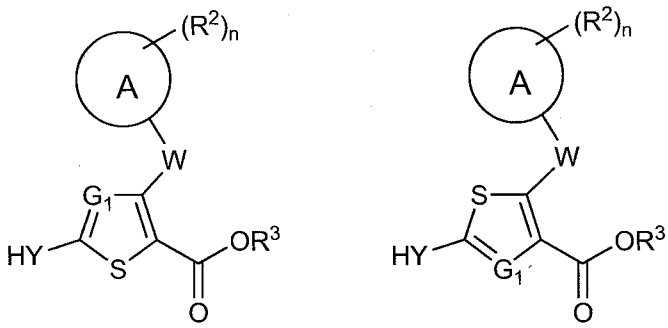
c) the compound is other than:





, or

[0017] In yet another embodiment of the invention, compounds of this invention are represented by formula **IA-i** or **IB-i**:



IA-i **IB-i**

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, or:

two adjacent R^2 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having

1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen, $-N(R^{7b})_2$, or an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

W is selected from a covalent bond, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7c}$, $-SR^{7a}$, or F;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

each occurrence of R^{7c} is independently an optionally substituted C_{1-6}aliphatic or an optionally substituted 3-7 membered cycloalphatic; or

wherein any two occurrences of R^7, R^{7a}, R^{7b} , or R^{7c}, taken together with atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

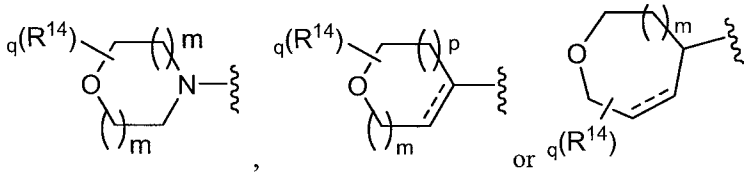
G_1 is N or $-CR^8$, wherein R^8 is H, –CN, halogen, $–Z_2-R^9$, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2$-, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$,

$-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, or -OC(O)-;

R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

HY is 

;

====== represents a single bond or a double bond;

wherein each occurrence of R^{14} is independently–R^{14a} or -T_1-R^{14d}, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, -NO_2, -R^{14c}, -$N(R^{14b})_2$, -OR^{14b}, -SR^{14c}, -$S(O)_2R^{14c}$, -$C(O)R^{14b}$, -$C(O)OR^{14b}$, -$C(O)N(R^{14b})_2$, -$S(O)_2N(R^{14b})_2$, -$OC(O)N(R^{14b})_2$, -$N(R^{14e})C(O)R^{14b}$, -$N(R^{14e})SO_2R^{14c}$, -$N(R^{14e})C(O)OR^{14b}$, -$N(R^{14e})C(O)N(R^{14b})_2$, or –$N(R^{14e})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

T_1 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by -$N(R^{14a})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -$C(O)N(R^{14a})$-, -$S(O)_2N(R^{14a})$-, -$OC(O)N(R^{14a})$-, -$N(R^{14a})C(O)$-, -$N(R^{14a})SO_2$-, -$N(R^{14a})C(O)O$-, -$NR^{14a}C(O)N(R^{14a})$-, -$N(R^{14a})S(O)_2N(R^{14a})$-, -OC(O)-, or -$C(O)N(R^{14a})$-O- or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

n is 0-6;

q is 0-4;

m is 1 or 2; and

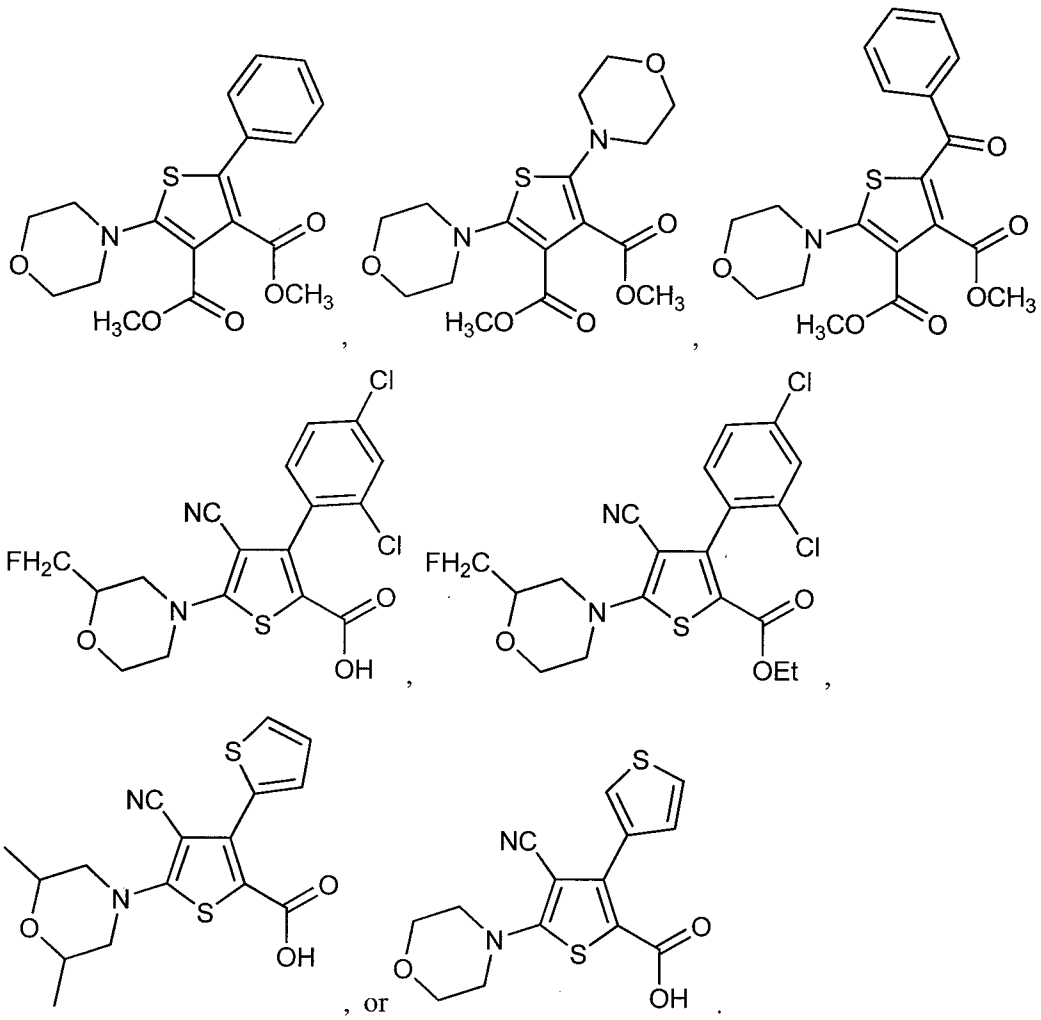
p is 0, 1, or 2;

provided that:

a) when G_1 is C-CN, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

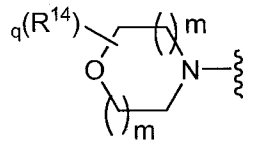
b) when G_1 is N, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

c) the compound is other than:



[0018] In some embodiments for compounds described directly above, G_1 is N.

[0019] In some embodiments for compounds described directly above, G_1 is $C(R^8)$, wherein R^8 is –CN or C_{2-4} alkynyl.

[0020] In some embodiments for compounds described directly above, HY is , wherein both occurrences of m are 1.

[0021] In some embodiments for compounds described directly above, R^3 is H.

DETAILED DESCRIPTION OF THE INVENTION

[0022] *2. Compounds and Definitions:*

[0023] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. It will be appreciated that preferred subsets described for each variable herein can be used for any of the structural subsets as well. As used herein, the following definitions shall apply unless otherwise indicated.

[0024] As described herein, compounds of the invention may be optionally substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, means that a hydrogen radical of the designated moiety is replaced with the radical of a specified substituent, provided that the substitution results in a stable or chemically feasible compound. The term "substitutable", when used in reference to a designated atom, means that attached to the atom is a hydrogen radical, which hydrogen atom can be replaced with the radical of a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds.

[0025] A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature from about –80°C to about +40°, in the absence of moisture or other chemically reactive conditions, for at least a week, or a compound which maintains its integrity long enough to be useful for therapeutic or prophylactic administration to a patient.

[0026] The phrase "one or more substituents", as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites, provided that the above conditions of stability and chemical feasibility are met.

[0027] As used herein, the term "independently selected" means that the same or different values may be selected for multiple instances of a given variable in a single compound.

[0028] As used herein, "a 3-7-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10-membered partially unsaturated, or aromatic bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur" includes cycloaliphatic, heterocyclic, aryl and heteroaryl rings.

[0029] As used herein, the term "aromatic" includes aryl and heteroaryl groups as described generally below and herein.

[0030] The term "aliphatic" or "aliphatic group", as used herein, means an optionally substituted straight-chain or branched C_{1-12} hydrocarbon, or a cyclic C_{1-12} hydrocarbon which is completely saturated or which contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle", "cycloaliphatic", "cycloalkyl", or "cycloalkenyl"). For example, suitable aliphatic groups include optionally substituted linear, branched or cyclic alkyl, alkenyl, alkynyl groups and hybrids thereof, such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl, or (cycloalkyl)alkenyl. Unless otherwise specified, in various embodiments, aliphatic groups have 1–12, 1–10, 1–8, 1–6, 1–4, 1–3, or 1-2 carbon atoms.

[0031] The term "alkyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having 1–12, 1–10, 1–8, 1–6, 1–4, 1–3, or 1-2 carbon atoms.

[0032] The term "alkenyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one double bond and having 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms.

[0033] The term "alkynyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one triple bond and having 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms.

[0034] The terms "cycloaliphatic", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic", used alone or as part of a larger moiety, refer to an optionally substituted saturated or partially unsaturated cyclic aliphatic ring system having from 3 to about 14 ring carbon atoms. In some embodiments, the cycloaliphatic group is an optionally substituted monocyclic hydrocarbon having 3-8 or 3-6 ring carbon atoms. Cycloaliphatic groups include, without limitation, optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, or cyclooctadienyl. The terms "cycloaliphatic", "carbocycle", "carbocyclyl", "carbocyclo",

or "carbocyclic" also include optionally substituted bridged or fused bicyclic rings having 6-12, 6-10, or 6-8 ring carbon atoms, wherein any individual ring in the bicyclic system has 3-8 ring carbon atoms.

[0035] The term "cycloalkyl" refers to an optionally substituted saturated ring system of about 3 to about 10 ring carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0036] The term "cycloalkenyl" refers to an optionally substituted non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and having about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopentyl, cyclohexenyl, and cycloheptenyl.

[0037] The terms "haloaliphatic", "haloalkyl", "haloalkenyl" and "haloalkoxy" refer to an aliphatic, alkyl, alkenyl or alkoxy group, as the case may be, which is substituted with one or more halogen atoms. As used herein, the term "halogen" or "halo" means F, Cl, Br, or I. The term "fluoroaliphatic" refers to a haloaliphatic wherein the halogen is fluoro, including perfluorinated aliphatic groups. Examples of fluoroaliphatic groups include, without limitation, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1,1,2-trifluoroethyl, 1,2,2-trifluoroethyl, and pentafluoroethyl.

[0038] The term "heteroatom" refers to one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0039] The terms "aryl" and "ar-", used alone or as part of a larger moiety, e.g., "aralkyl", "aralkoxy", or "aryloxyalkyl", refer to an optionally substituted C_{6-14}aromatic hydrocarbon moiety comprising one to three aromatic rings. Preferably, the aryl group is a C_{6-10}aryl group. Aryl groups include, without limitation, optionally substituted phenyl, naphthyl, or anthracenyl. The terms "aryl" and "ar-", as used herein, also include groups in which an aryl ring is fused to one or more cycloaliphatic rings to form an optionally substituted cyclic structure such as a tetrahydronaphthyl, indenyl, or indanyl ring. The term "aryl" may be used interchangeably with the terms "aryl group", "aryl ring", and "aromatic ring".

[0040] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently attached to an alkyl group, either of which independently is optionally substituted. Preferably, the aralkyl group is C_{6-10} arylC_{1-6}alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0041] The terms "heteroaryl" and "heteroar-", used alone or as part of a larger moiety, e.g., "heteroaralkyl", or "heteroaralkoxy", refer to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. A heteroaryl group may be mono-, bi-, tri-, or polycyclic, preferably

mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. For example, a nitrogen atom of a heteroaryl may be a basic nitrogen atom and may also be optionally oxidized to the corresponding N-oxide. When a heteroaryl is substituted by a hydroxy group, it also includes its corresponding tautomer. The terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocycloaliphatic rings. Nonlimiting examples of heteroaryl groups include thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic", any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0042] As used herein, the terms "heterocycle", "heterocyclyl", "heterocyclic radical", and "heterocyclic ring" are used interchangeably and refer to a stable 3- to 8-membered monocyclic or 7–10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl), or NR^+ (as in N-substituted pyrrolidinyl).

[0043] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and thiamorpholinyl. A heterocyclyl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted. Additionally, a heterocyclic ring also includes groups in which the heterocyclic ring is fused to one or more aryl rings.

[0044] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic (e.g., aryl or heteroaryl) moieties, as herein defined.

[0045] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. An optionally substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms is optionally replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group and also include those described in the specification herein. It will be appreciated that two substituents of the alkylene group may be taken together to form a ring system. In certain embodiments, two substituents can be taken together to form a 3-7-membered ring. The substituents can be on the same or different atoms.

[0046] An alkylene chain also can be optionally interrupted by a functional group. An alkylene chain is "interrupted" by a functional group when an internal methylene unit is interrupted by the functional group. Examples of suitable "interrupting functional groups" are described in the specification and claims herein.

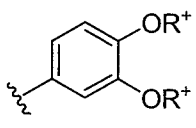
[0047] For purposes of clarity, all bivalent groups described herein, including, e.g., the alkylene chain linkers described above, are intended to be read from left to right, with a corresponding left-to-right reading of the formula or structure in which the variable appears.

[0048] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be "optionally substituted". In addition to the substituents defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group also include and are generally selected from -halo, $-NO_2$, -CN, $-R^+$, $-C(R^+)=C(R^+)_2$, $-C\equiv C-R^+$, $-OR^+$, $-SR^\circ$, $-S(O)R^\circ$, $-SO_2R^\circ$, $-SO_3R^+$, $-SO_2N(R^+)_2$, $-N(R^+)_2$, $-NR^+C(O)R^+$, $-NR^+C(S)R^+$, $-NR^+C(O)N(R^+)_2$, $-NR^+C(S)N(R^+)_2$, $-N(R^+)C(=NR^+)-N(R^+)_2$, $-N(R^+)C(=NR^+)-R^\circ$, $-NR^+CO_2R^+$, $-NR^+SO_2R^\circ$, $-NR^+SO_2N(R^+)_2$, $-O-C(O)R^+$, $-O-CO_2R^+$, $-OC(O)N(R^+)_2$, $-C(O)R^+$, $-C(S)R^\circ$, $-CO_2R^+$, $-C(O)-C(O)R^+$, $-C(O)N(R^+)_2$, $-C(S)N(R^+)_2$, $-C(O)N(R^+)-OR^+$, $-C(O)N(R^+)C(=NR^+)-N(R^+)_2$, $-N(R^+)C(=NR^+)-N(R^+)-C(O)R^+$, $-C(=NR^+)-N(R^+)_2$, $-C(=NR^+)-OR^+$, $-N(R^+)-N(R^+)_2$, $-C(=NR^+)-N(R^+)-OR^+$, $-C(R^\circ)=N-OR^+$, $-P(O)(R^+)_2$, $-P(O)(OR^+)_2$, $-O-P(O)-OR^+$, and $-P(O)(NR^+)-N(R^+)_2$, wherein R^+, independently, is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, cycloaliphatic, or heterocyclyl group, or two independent occurrences of R^+ are taken together with their intervening atom(s) to form an optionally substituted 5-7-membered aryl, heteroaryl, cycloaliphatic, or heterocyclyl ring. Each R° is an optionally substituted aliphatic, aryl, heteroaryl, cycloaliphatic, or heterocyclyl group.

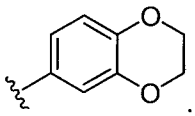
[0049] An aliphatic or heteroaliphatic group, or a non-aromatic carbycyclic or heterocyclic ring may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic carbocyclic or heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, $=C(R^*)_2$, $=N-N(R^*)_2$, =N-OR*, =N-NHC(O)R*, $=N-NHCO_2R^\circ$ $=N-NHSO_2R^\circ$ or =N-R* where R° is defined above, and each R* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group.

[0050] In addition to the substituents defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring also include and are generally selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-C(O)OR^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-S(O)_2R^+$, $-S(O)_2N(R^+)_2$, $-C(S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-N(R^+)S(O)_2R^+$; wherein each R^+ is defined above. A ring nitrogen atom of a heteroaryl or non-aromatic heterocyclic ring also may be oxidized to form the corresponding N-hydroxy or N-oxide compound. A nonlimiting example of such a heteroaryl having an oxidized ring nitrogen atom is N-oxidopyridyl.

[0051] As detailed above, in some embodiments, two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) to form a monocyclic or bicyclic ring selected from 3–13-membered cycloaliphatic, 3–12-membered heterocyclyl having 1–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6–10-membered aryl, or 5–10-membered heteroaryl having 1–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0052] Exemplary rings that are formed when two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) include, but are not limited to the following: a) two independent occurrences of R^+ (or any other variable similarly defined in the specification or claims herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^+)_2$, where both occurrences of R^+ are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^+ (or any other variable similarly defined in the specification or claims herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR^+ 

, these two occurrences of R^+ are taken together with the oxygen atoms to which they are bound to form a fused 6-

membered oxygen containing ring: . It will be appreciated that a variety of other rings (e.g., spiro and bridged rings) can be formed when two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein) are taken together with their intervening atom(s) and that the examples detailed above are not intended to be limiting.

[0053] Exemplary rings that are formed when two independent occurrences of $R^{3'}$ or R^4 are taken together with their intervening atom(s) include, but are not limited to the following: indolizinyl, imidazopyridyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, 4H-furo[3,2-b]pyrrolyl, pyrazolopyrimidinyl, purinyl, and pyrrolizinyl.

[0054] Exemplary rings that are formed when two independent occurrences of R^7, R^{7a}, or R^{7b} are taken together with their intervening atom(s) include, but are not limited to the following: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, oxazolidinyl, piperazinyl, dioxanyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, and thiomorpholinyl.

[0055] Exemplary rings that are formed when two independent occurrences of R^{7a} and R^2, or R^{7b} and R^2 are taken together with their intervening atom(s) include, but are not limited to the following: isoindolyl, indazolyl, benzothienyl, dihydrobenzothienyl, isobenzofuranyl, benzoisoxazolyl, dihydroisobenzofuranyl, pyrazolopyrimidinyl, pyrazolopyridinyl, isoquinolyl, tetrahydroisoquinolinyl, phthalazinyl, isochromanyl, isothiochromanyl, isoindolinyl, and benzoisothiazolyl.

[0056] Exemplary rings that are formed when two independent occurrences of X_4 and X_5, or X_6 and X_7; are taken together with their intervening atom(s) include, but are not limited to the following: pyrazolopyrimidinyl, purinyl, quinolyl, tetrahydroquinolinyl, quinazolinyl, naphthyridinyl, pyridopyrimidinyl, pyrazolopyridinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, imidazopyridinyl, 1H-pyrrolo[2,3-b]pyridinyl-2(3H)-one, 3,4-dihydro-1,8-naphthyridinyl-2(1H)-one, 1,8-naphthyridinyl-2(1H)-one, 1H-pyridyl[2,3-d][1,3]oxazin-2(4H)-one, 1H-imidazo[4,5-b]pyridyl-2(3H)-one, oxazolo[4,5-b]pyridyl-2(3H)-one, 1,2-dihydropyridyl[2,3-b]pyrazin-3(4H)-one, 2H-pyridyl[3,2-b][1,4]oxazin-3(4H)-one, 3,4-dihydropyridyl[2,3-d]pyrimidin-2(1H)-one, imidazopyridinyl, and tetrahydroquinazolinyl.

[0057] Exemplary rings that are formed when two independent occurrences of Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 are taken together with their intervening atom(s) include, but are not limited to the following: indolyl, indazolyl, 4H-furo[3,2-b]pyrrolyl, 4H-thieno[3,2-b]pyrrolyl, 5H-furo[2,3-b]pyrrolyl, 5H-thieno[2,3-b]pyrrolyl, pyrrolo[3,4-b]pyrrolyl, pyrrolo[3,2-b]pyrrolyl, pyrrolo[2,3-b]pyrrolyl,

dihydropyrrolo[3,2-b]pyrrolyl, dihydropyrrolo[2,3-b]pyrrolyl, 5H-pyrrolo[3,2-d]oxazole, 5H-pyrrolo[3,2-d]thiazole, pyrrolopyrimidinyl, pyrrolopyridinyl, pyrazolopyrimidinyl and pyrazolopyridinyl.

[0058] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures where there is a replacement of hydrogen by deuterium or tritium, or a replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, as a nonlimiting example, as analytical tools or probes in biological assays.

[0059] It is to be understood that, when a disclosed compound has at least one chiral center, the present invention encompasses one enantiomer of inhibitor free from the corresponding optical isomer, racemic mixture of the inhibitor and mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a mixture is enriched in one enantiomer relative to its optical isomers, the mixture contains, for example, an enantiomeric excess of at least 50%, 75%, 90%, 95% 99% or 99.5%.

[0060] The enantiomers of the present invention may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. Where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

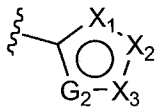
[0061] When a disclosed compound has at least two chiral centers, the present invention encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diasteromeric pairs, mixtures of diasteromers, mixtures of diasteromeric pairs, mixtures of diasteromers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diasteromeric

pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s). When a mixture is enriched in one diastereomer or diastereomeric pair(s) relative to the other diastereomers or diastereomeric pair(s), the mixture is enriched with the depicted or referenced diastereomer or diastereomeric pair(s) relative to other diastereomers or diastereomeric pair(s) for the compound, for example, by a molar excess of at least 50%, 75%, 90%, 95%, 99% or 99.5%.

[0062] The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. Specific procedures for chromatographically separating diastereomeric pairs of precursors used in the preparation of compounds disclosed herein are provided the examples herein.

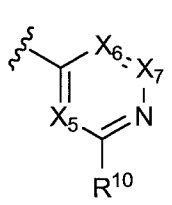
[0063] *3. Description of Exemplary Compounds:*

[0064] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**, CY is:

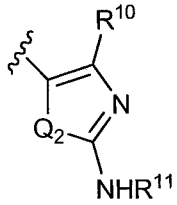


[0065] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, X_1 is N, G_2 is -N($R^{3'}$)-, and X_2 and X_3 are CH. In certain other embodiments, X_1 and X_2 are N, G_2 is -N($R^{3'}$)-, and X_3 is CH. In certain other embodiments, X_3 is N, G_2 is -N($R^{3'}$)-, and X_1 and X_2 are CH. In certain other embodiments, X_1 is N, X_2 is CH, X_3 is –N($R^{3'}$)- and G_2 is =N-.

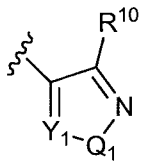
[0066] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, HY is selected from:



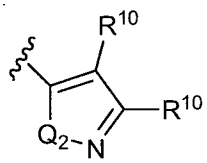
H,



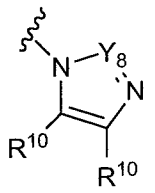
J,



K,



L, or



M;

wherein each occurrence of X_5, X_6, and X_7 is independently –CR^{10} or N, provided no more than

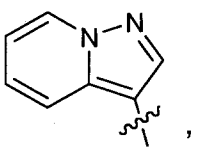
two occurrences of X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $-NR^5$;

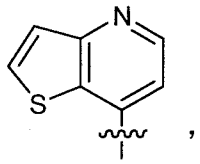
each occurrence of Y_1 and Y_7 is independently $-CR^{10}$ or N;

or wherein two adjacent occurrences of X_6 and X_7, or Y_1 and Q_1, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

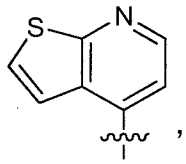
[0067] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, HY is selected from:



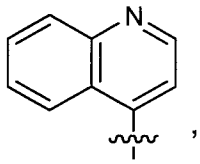
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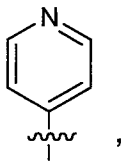
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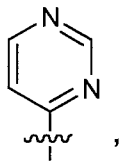
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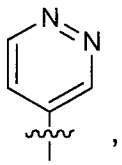
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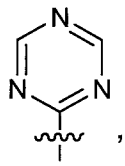
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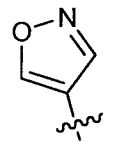
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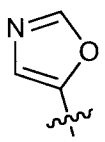
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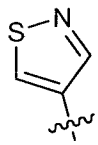
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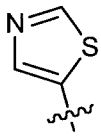
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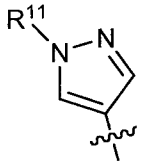
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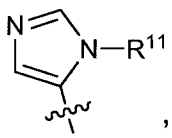
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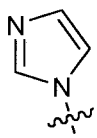
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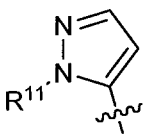
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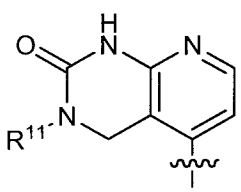
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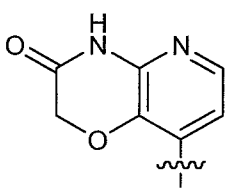


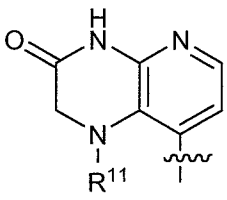
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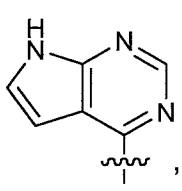


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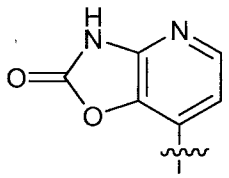
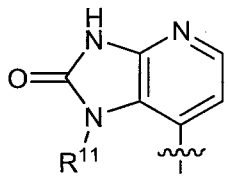
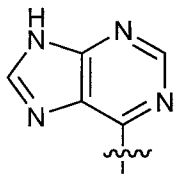
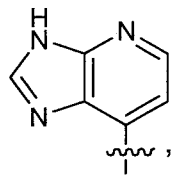




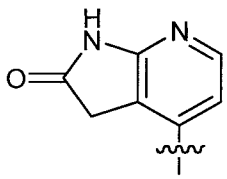
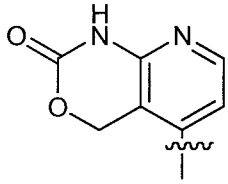
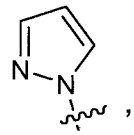




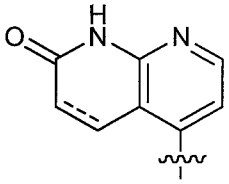
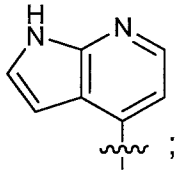
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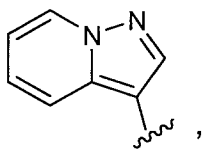
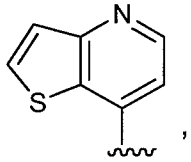
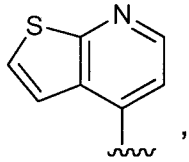
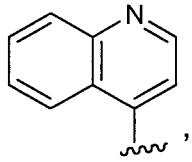
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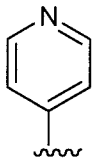
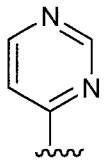
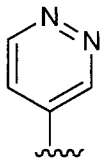
xxviii xxix

wherein each HY group is optionally additionally substituted with one or more occurrences of R^{10}, and ====== in **xviii** represents a single bond or a double bond.

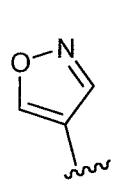
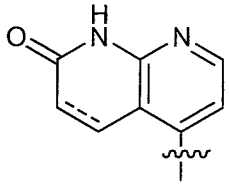
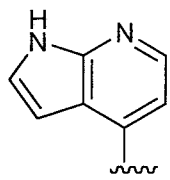
[0068] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a,**, HY is selected from:


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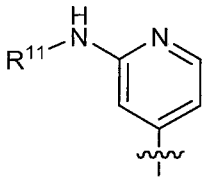
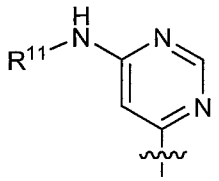
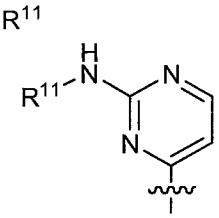
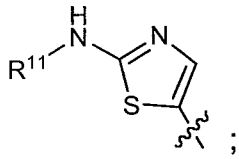
i ii iii iv


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v vi vii

ix **xxviii** **xxix**;

xxx **xxxi** **xxxii** **xxxiii**

wherein each HY group is optionally additionally substituted with one or more occurrences of R^{10}, and ====== in **xviii** represents a single bond or a double bond.

[0069] In yet other embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, G_1 is $C(R^8)$. In other embodiments, G_1 is CH.

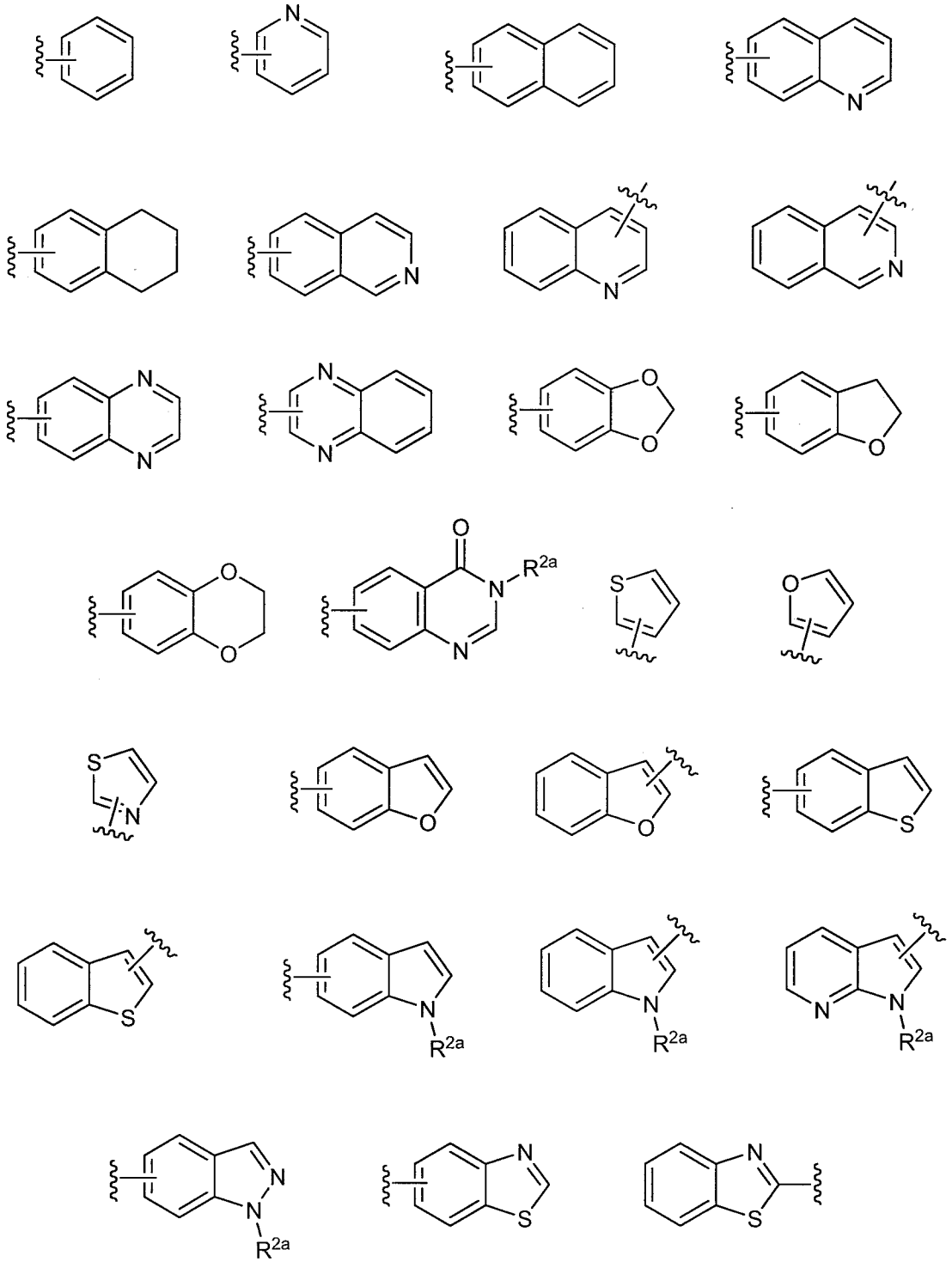
[0070] In still other embodiments, G_1 is N.

[0071] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,W is -$C(R^7)_2$-, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN; and wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, -$C(O)R^{7a}$, or -$S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring.

[0072] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, W is –$C(H)(N(R^{7b})_2)$-, -CH_2-, -$C(H)(OR^{7a})$-, -NR^{7b}-, or –$N(R^{7a})C(O)$-, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[0073] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

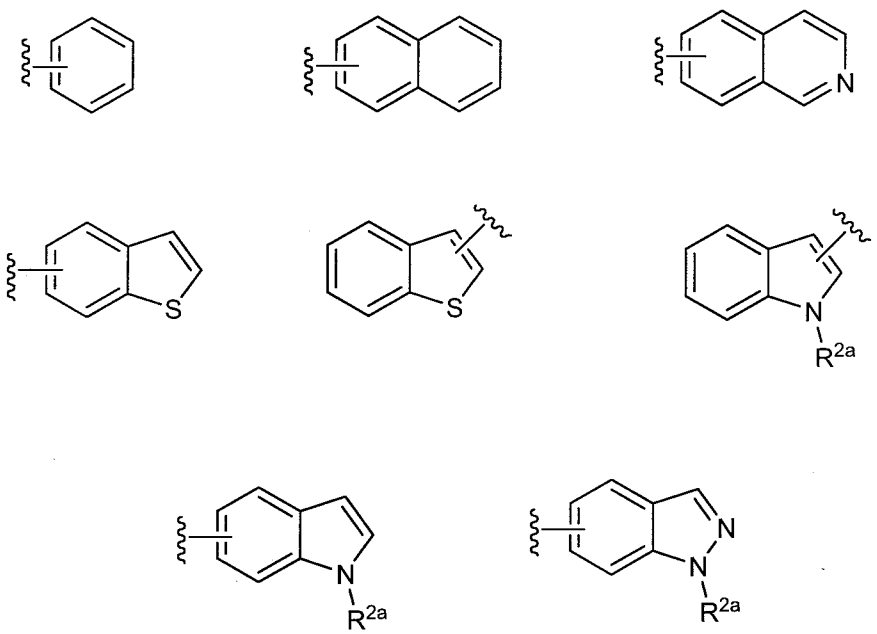
[0074] In other embodiments, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0075] In certain other embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0076] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

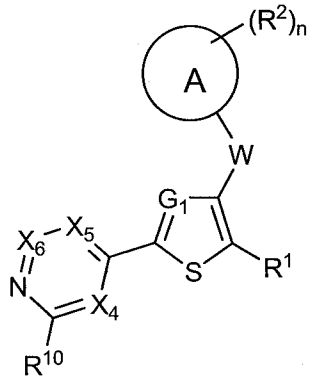
[0077] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[0078] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3}

alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[0079] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[0080] In still other embodiments, a compound having the structure of formula **II** is provided:



II

wherein:

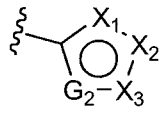
X_4, X_5 and X_6 are each independently $-CR^{10}$ or N, provided no more than two occurrences of X_4, X_5 and X_6 are N;

or two adjacent groups selected from R^{10}, X_4, X_5, and X_6, taken together, form an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0081] In some embodiments, for compounds of formula **II**, one of X^4, X^5, or X^6 is N.

[0082] In still other embodiments, for compounds of formula **II**, all of X^4, X^5, or X^6 are CR^{10}.

[0083] In other embodiments, for compounds of formula **II**, each occurrence of R^{10} is independently selected from –CN, $-OR^{10a}$, $-N(R^{11})_2$, halogen, C_{1-4}alkyl, $-N(R^{11})COR^{10a}$, or wherein two occurrences of R^{10}, taken together with the atoms to which they are bound form an optionally substituted group selected from a fused 5- or 6-membered cycloaliphatic, 4-10-membered heterocyclyl, 6-10-membered aryl or 5-10-membered heteroaryl ring, wherein the heterocyclyl and heteroaryl rings have 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0084] In some other embodiments, for compounds of formula **II**, CY is 

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[0085] In some other embodiments, for compounds of formula **II**, X_1 is N, G_2 is $-N(R^{3'})-$, and X_2 and X_3 are CH.

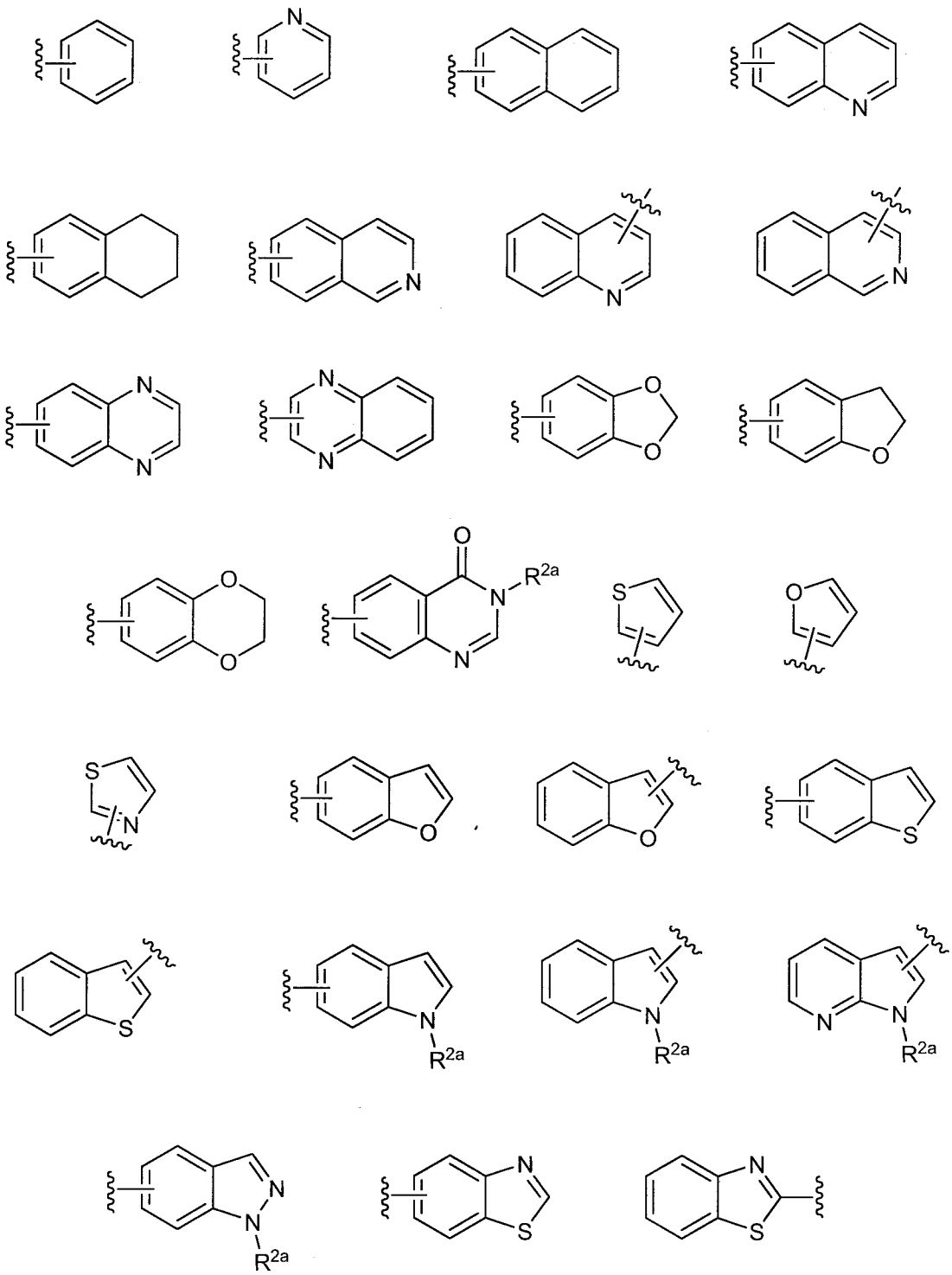
[0086] In some other embodiments, for compounds of formula **II**, X_1 and X_2 are N, G_2 is -N($R^{3'}$)-, and X_3 is CH.

[0087] In some other embodiments, for compounds of formula **II**, X_3 is N, G_2 is -N($R^{3'}$)-, and X_1 and X_2 are CH.

[0088] In some other embodiments, for compounds of formula **II**, X_1 is N, X_2 is CH, X_3 is –N($R^{3'}$)- and G_2 is =N-.

[0089] In some other embodiments, for compounds of formula **II**, Ring A is an optionally substituted 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

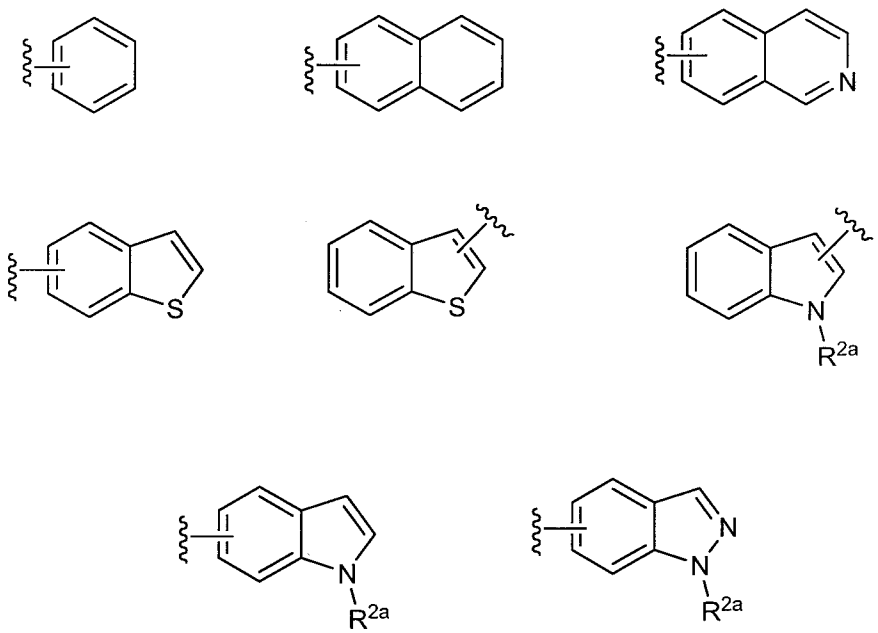
[0090] In other embodiments, for compounds of formula **II**, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0091] In certain other embodiments, for compounds of general formula **II**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0092] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -NHS(O)$_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[0093] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[0094] In some other embodiments, for compounds of formula **II**, Ring A is a phenyl group optionally substituted with 1-3 independent occurrences of halogen, C_{1-3} alkyl, -CN, C_{1-3}haloalkyl,

-OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, $NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[0095] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[0096] In some other embodiments, for compounds of formula **II**, W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is selected from hydrogen, optionally substituted C_{1-4} aliphatic, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or –CN; and

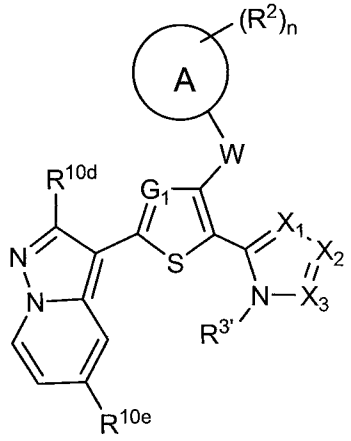
wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0097] In some other embodiments, for compounds of formula **II**, W is $–C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, or $–N(R^{7a})C(O)-$, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[0098] In still other embodiments, a compound having the structure of formula **III** is provided:



III

wherein R^{10d} is hydrogen or optionally substituted C_{1-4}alkyl, and R^{10e} is R^{10}.

[0099] In some other embodiments, for compounds of formula **III**, R^{10e} is $-T_1-R^{10b}$, or hydrogen.

[00100] In still other embodiments, for compounds of formula **III**, R^{10e} is hydrogen, $-CH_2N(R^{11})_2$, or $-CH_2N(R^{11})C(=NR^{11})N(R^{11})_2$, wherein R^{11} is $-C(O)R^{11a}$, an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00101] In some other embodiments, for compounds of formula **III**, R^{11} is an optionally substituted C_{1-6} aliphatic group, the C_{1-6} aliphatic group is further defined as $-(CH_2)_xR^{11b}$ or $-(CH_2)_xN(R^{11b})_2$, $-(CH_2)_xN(R^{11b})C(O)R^{11b}$, or $-(CH_2)_xN(R^{11b})C(O)OR^{11b}$, wherein R^{11b} is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and x is 1 to 3.

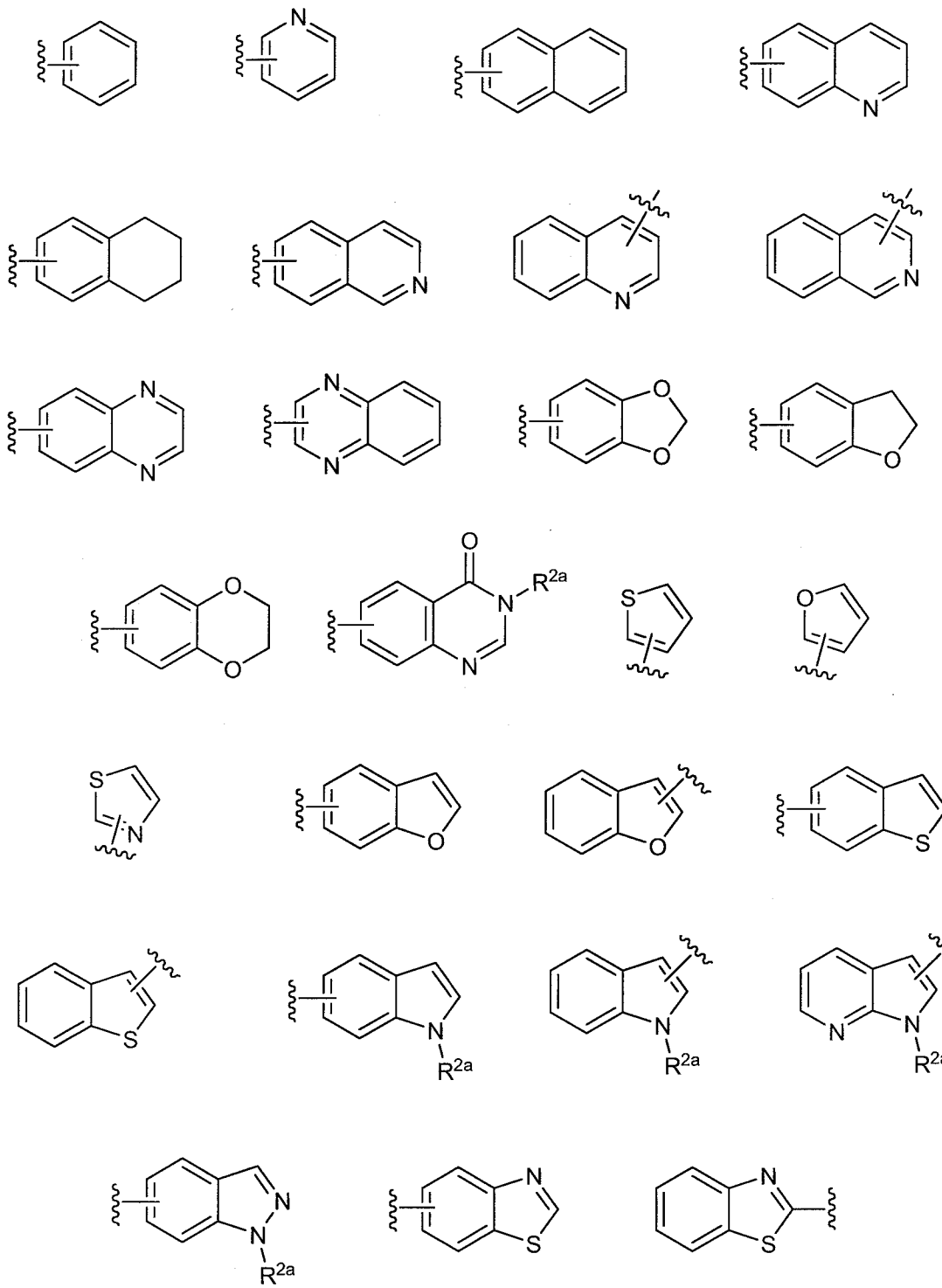
[00102] In some other embodiments, for compounds of formula **III**, X_1 is N, and X_2 and X_3 are CH.

[00103] In some other embodiments, for compounds of formula **III**, X_1 and X_2 are N, and X_3 is CH.

[00104] In some other embodiments, for compounds of formula **III**, X_3 is N, and X_1 and X_2 are CH.

[00105] In some other embodiments, for compounds of formula **III**, Ring A is an optionally substituted 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

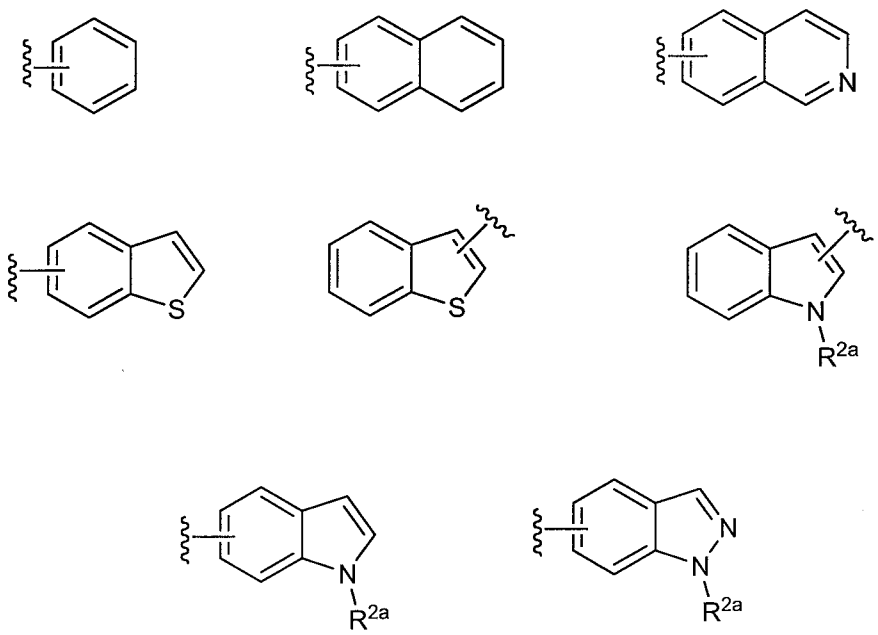
[00106] In other embodiments, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00107] In certain other embodiments, for compounds of general formula **III**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00108] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00109] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00110] In some other embodiments, for compounds of formula **III**, Ring A is a phenyl group optionally substituted with 1-3 independent occurrences of halogen, C_{1-3} alkyl, -CN, C_{1-3}haloalkyl, -OC_{1-3}

alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00111] In some other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00112] In some other embodiments, for compounds of formula **III**, W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is selected from hydrogen, optionally substituted C_{1-4} aliphatic, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or -CN; and

wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic;

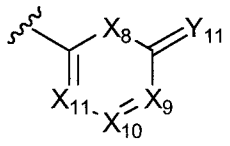
each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

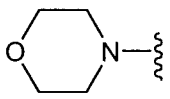
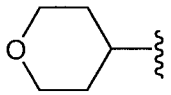
[00113] In some other embodiments, for compounds of formula **III**, W is $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, or $-N(R^{7a})C(O)-$, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00114] In certain embodiments, for compounds of general formula **IA-a**, **IB-a, IA, IB, II or III**, CY is:



[00115] In certain embodiments, for compounds of general formula IA-a, IB-a, IA, IB, II or III, X_8 and X_{11} are N, X_9 and X_{10} are CR^4, and Y_{11} is O.

[00116] In certain embodiments, for compounds of general formula **IA-a**, **IB-a, IA, IB, II or III**, HY is selected from:


and

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wherein each HY group is optionally additionally substituted with one or more occurrences of R^{14}.

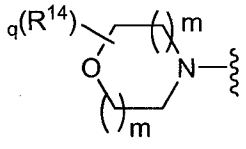
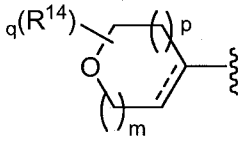
[00117] In yet other embodiments, for compounds of general formula **IA-a, IB-a, IA, IB, II or III**, G_1 is N.

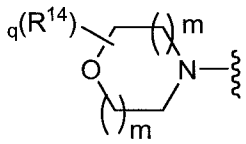
[00118] In still other embodiments, for compounds of general formula **IA-a, IB-a, IA, IB, II or III**, R^1 is -C(O)OH.

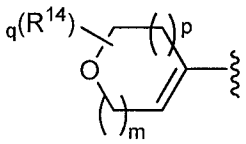
[00119] In certain other embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,** R^3 is H. In certain other embodiments, R^3 is C_{1-6} aliphatic. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is methyl or ethyl.

[00120] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,** G_1 is N. In certain other embodiments, G_1 is $C(R^8)$. In certain embodiments, G_1 is $C(R^8)$ and R^8 is –CN, halogen, or C_{1-6} aliphatic. In certain embodiments, R^8 is C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl. In certain embodiments, R^8 is –CN or C_{2-4} alkynyl.

[00121] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** HY is selected from:


or

.


[00122] In certain embodiments, HY is wherein each occurrence of m is 1 and q is 0 or 1. In certain embodiments, q is 0.


[00123] In certain embodiments, HY is wherein m and p are 1 and q is 0 or 1. In certain embodiments, q is 0.

[00124] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-N(R^{7b})_2$, or F; and each occurrence of R^{7b} is independently hydrogen,

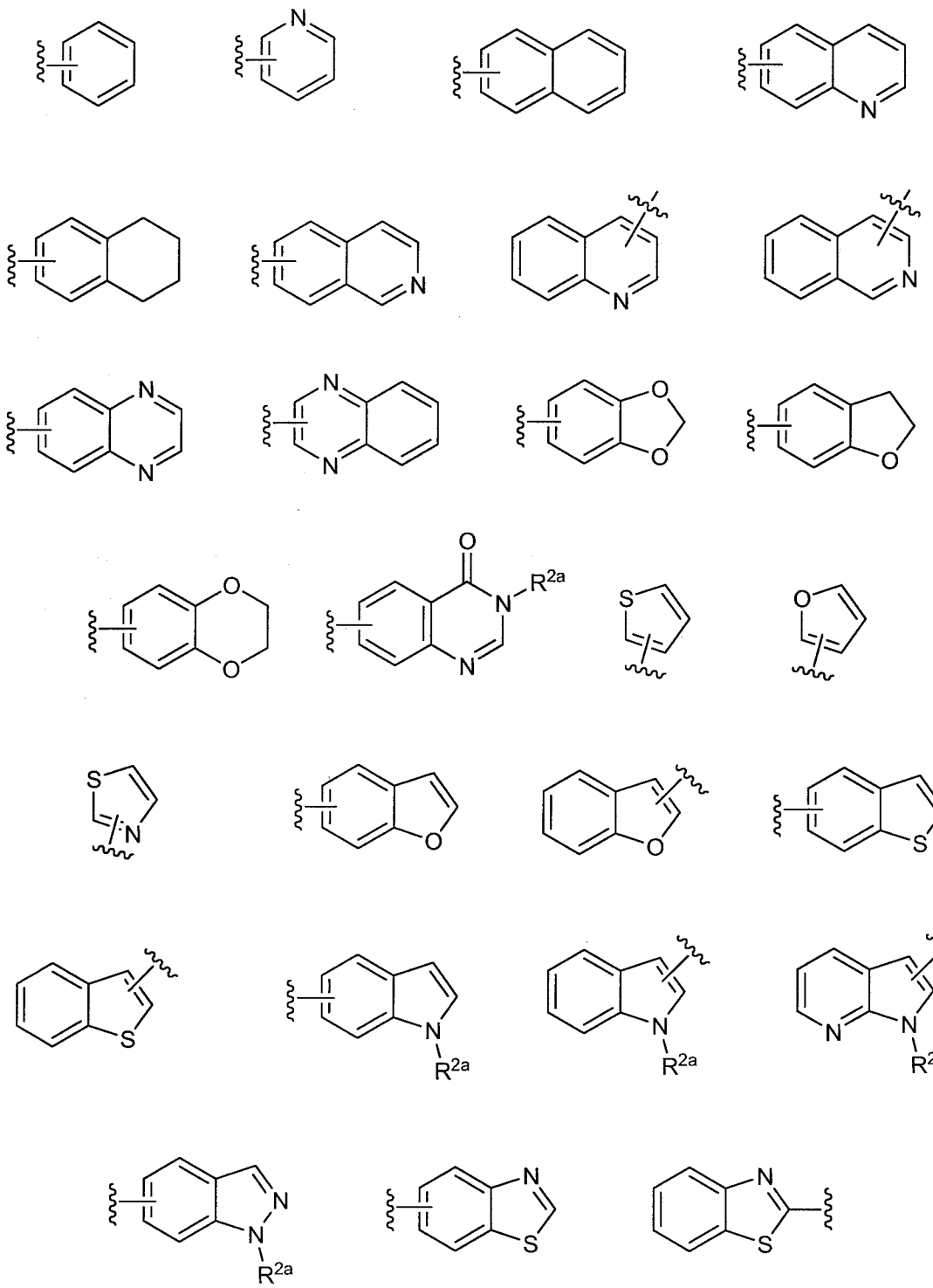
optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring; and wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00125] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** W is $-C(H)(N(R^{7b})_2)-$ or $-CH_2-$, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00126] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** W is a covalent bond.

[00127] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

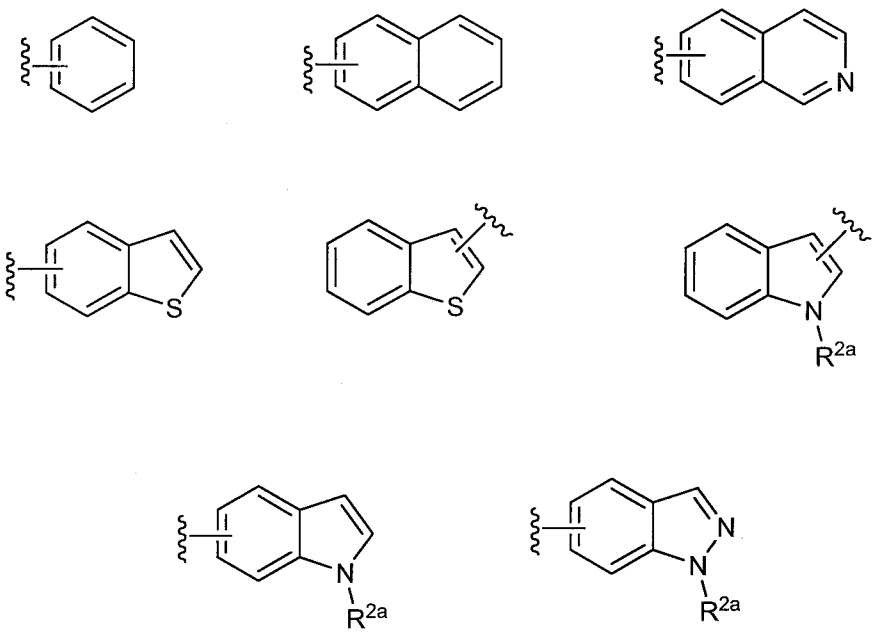
[00128] In other embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,** ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00129] In certain other embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00130] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00131] In yet other embodiments, ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00132] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00133] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-C(H)(N(R^{7b})_2)-$ or $-CH_2-$, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic. In certain embodiments, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-CH_2-$.

[00134] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00135] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, or $-T_2-R^{12d}$, T_2 is an optionally substituted C_{1-6} alkylene chain, R^{12d} is $-N(R^{7b})_2$, and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

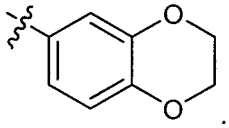
[00136] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OC_{1-3}$ alkyl, or $-OC_{1-3}$ haloalkyl; and n is 0 to 3. In certain embodiments, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OCH_3$, or $-OCF_3$; and n is 0 to 3.

[00137] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00138] In still other embodiments, Ring A is a phenyl group, R^2 is halogen or $-(CH_2)N(R^{7b})_2$ and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 2.

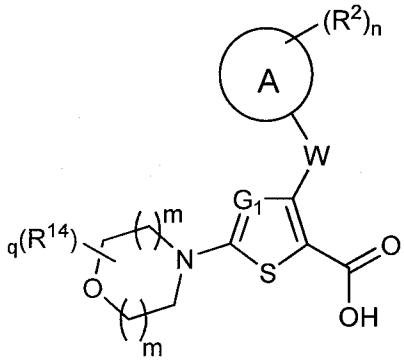
[00139] In certain embodiments, Ring A is a phenyl group, n is 1, and R^2 is in the para position. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the ortho and meta positions, and para with respect to each other.

[00140] In certain embodiments, Ring A is 2-chloro-5(dimethylaminomethyl)phenyl. In certain other embodiments, Ring A is 2-chloro-5(pyrrolidin-1-ylmethyl)phenyl.

[00141] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is a 2-naphthyl group. In certain other embodiments, Ring A is .

[00142] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring. In some embodiments, Ring A is substituted with one or more C_{1-3} alkyl groups.

[00143] In still other embodiments, a compound having the structure of formula **II-i** is provided:



II-i

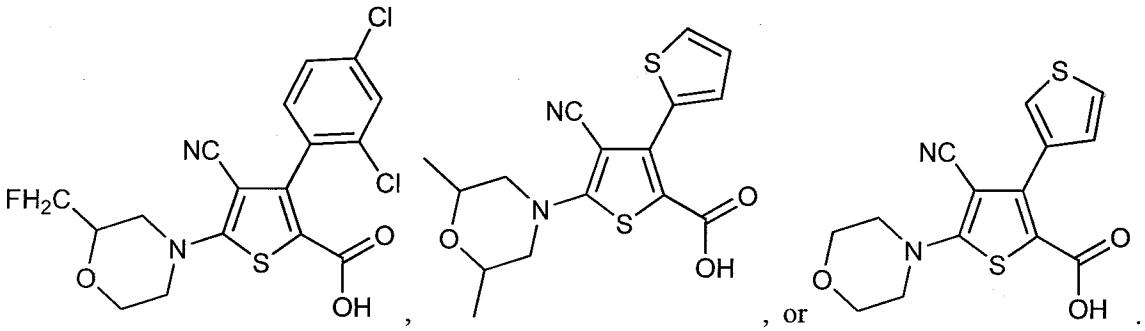
wherein Ring A, G_1, W, R^2, n, m, q, and R^{14} are as defined for the compounds described generally above and in subsets herein.

[00144] In certain embodiments, for compounds of general formula **II-i**:

a) when G_1 is C-CN, HY is unsubstituted morpholine, and W is a covalent bond, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

b) when G_1 is N, HY is unsubstituted morpholine, and W is a covalent bond, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

c) the compound is other than:



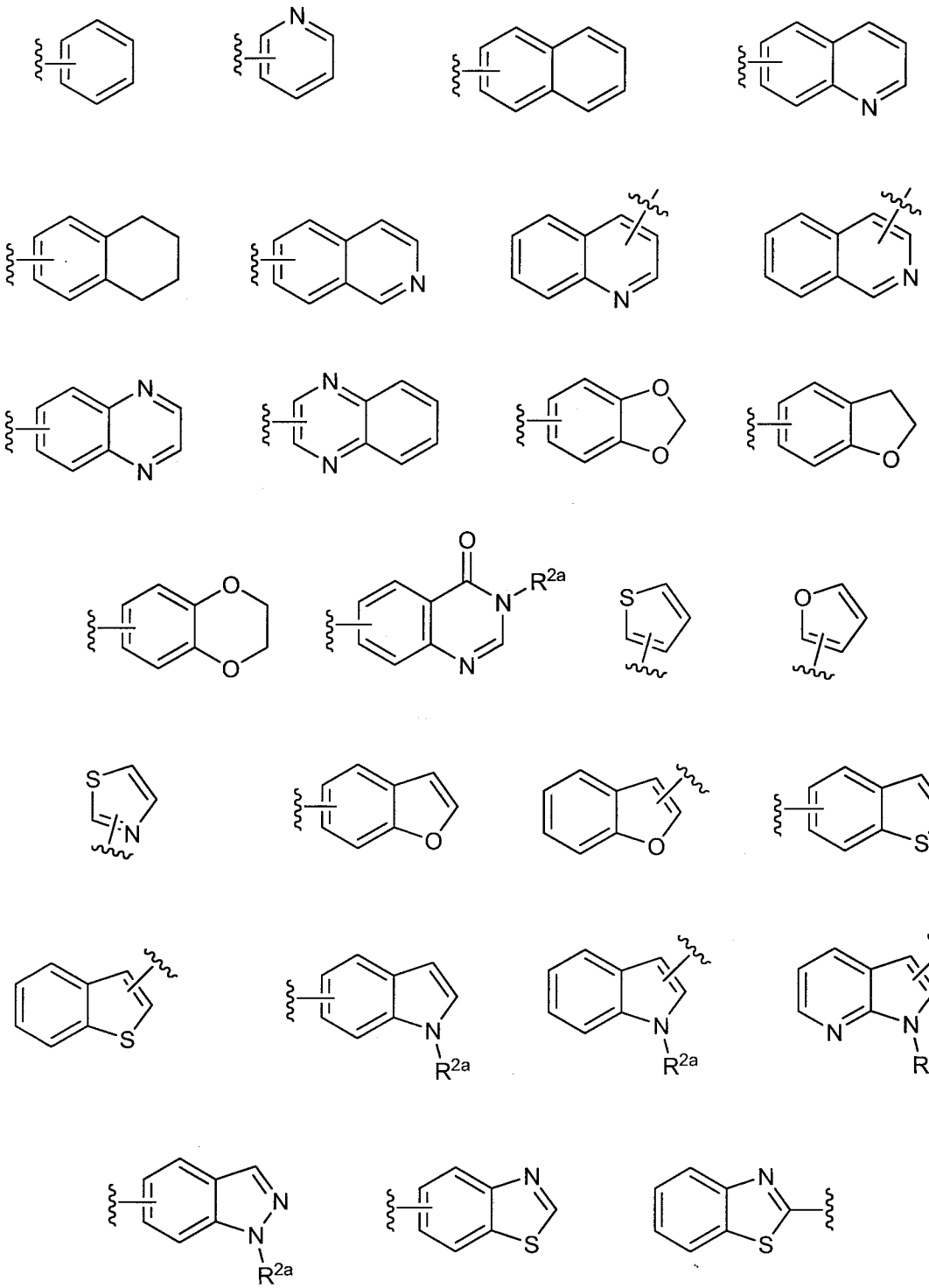
[00145] In certain embodiments, for compounds of general formula **II-i**, W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-N(R^{7b})_2$, or F; and wherein each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring; and each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00146] In certain embodiments, for compounds of general formula **II-i**, W is $-C(H)(N(R^{7b})_2)-$ or $-CH_2-$, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00147] In certain embodiments, for compounds of general formula **II-i**, W is a covalent bond.

[00148] In certain embodiments, for compounds of general formula **II-i**, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

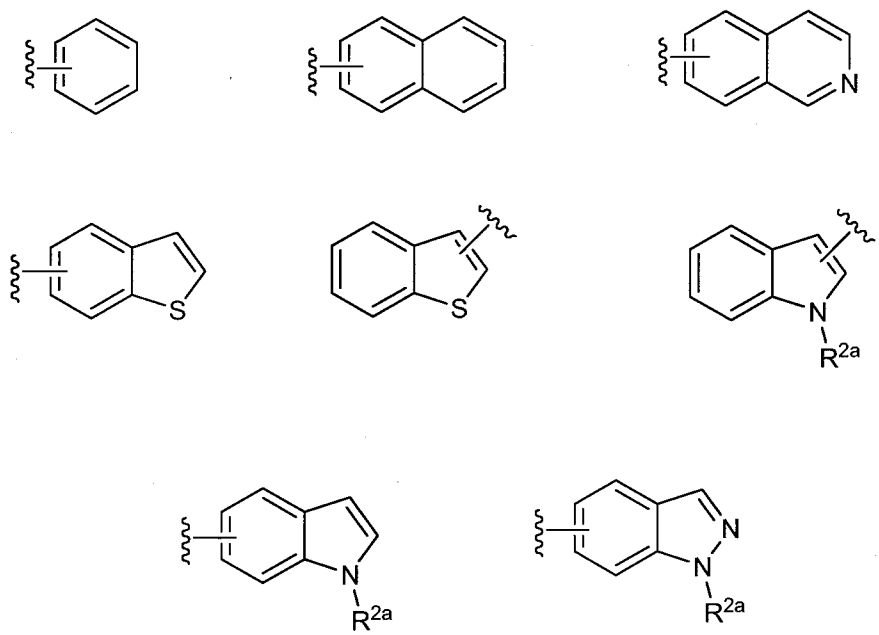
[00149] In other embodiments, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00150] In certain other embodiments, for compounds of general formula **II-i**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00151] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00152] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00153] In certain embodiments, for compounds of general formula **II-i**, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen,

or sulfur; n is 0 to 3, and W is $-C(H)(N(R^{7b})_2)-$ or $-CH_2-$, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic. In certain embodiments, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-CH_2-$.

[00154] In certain embodiments, for compounds of general formula **II-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl,

$-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00155] In certain embodiments, for compounds of general formula **II-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, or $-T_2-R^{12d}$, T_2 is an optionally substituted C_{1-6} alkylene chain, R^{12d} is $-N(R^{7b})_2$, and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

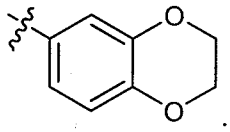
[00156] In certain embodiments, for compounds of general formula **II-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OC_{1-3}$ alkyl, or $-OC_{1-3}$ haloalkyl; and n is 0 to 3. In certain embodiments, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OCH_3$, or $-OCF_3$; and n is 0 to 3.

[00157] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00158] In still other embodiments, Ring A is a phenyl group, R^2 is halogen or $-(CH_2)N(R^{7b})_2$ and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 2.

[00159] In certain embodiments, Ring A is a phenyl group, n is 1, and R^2 is in the para position. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the ortho and meta positions, and para with respect to each other.

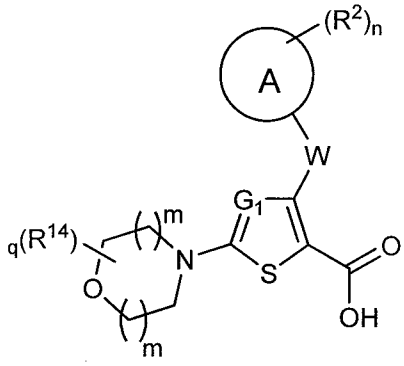
[00160] In certain embodiments, Ring A is 2-chloro-5(dimethylaminomethyl)phenyl. In certain other embodiments, Ring A is 2-chloro-5(pyrrolidin-1-ylmethyl)phenyl.

[00161] In certain embodiments, for compounds of general formula **II-i**, Ring A is a 2-naphthyl group. In certain other embodiments, Ring A is .

[00162] In certain embodiments, for compounds of general formula **II-i**, Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring. In some embodiments, Ring A is substituted with one or more C_{1-3} alkyl groups.

[00163] In certain embodiments, for compounds of general formula **II-i**, each occurrence of m is 1 and q is 0.

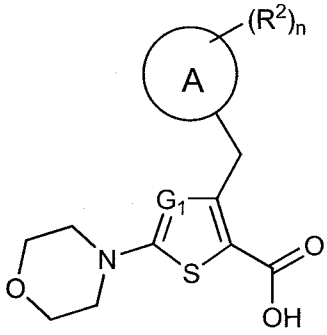
[00164] In still other embodiments, a compound having the structure of formula **II-i** is provided:



II-i

[00165] wherein G_1 is N or $-CR^8$, and R^8 is –CN; ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3; and W is $-C(R^7)_2-$, or >=O, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-OR^{7a}$, $-N(R^{7b})_2$, or F; and wherein each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring; and each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00166] In still other embodiments, a compound having the structure of formula **III-i** is provided:

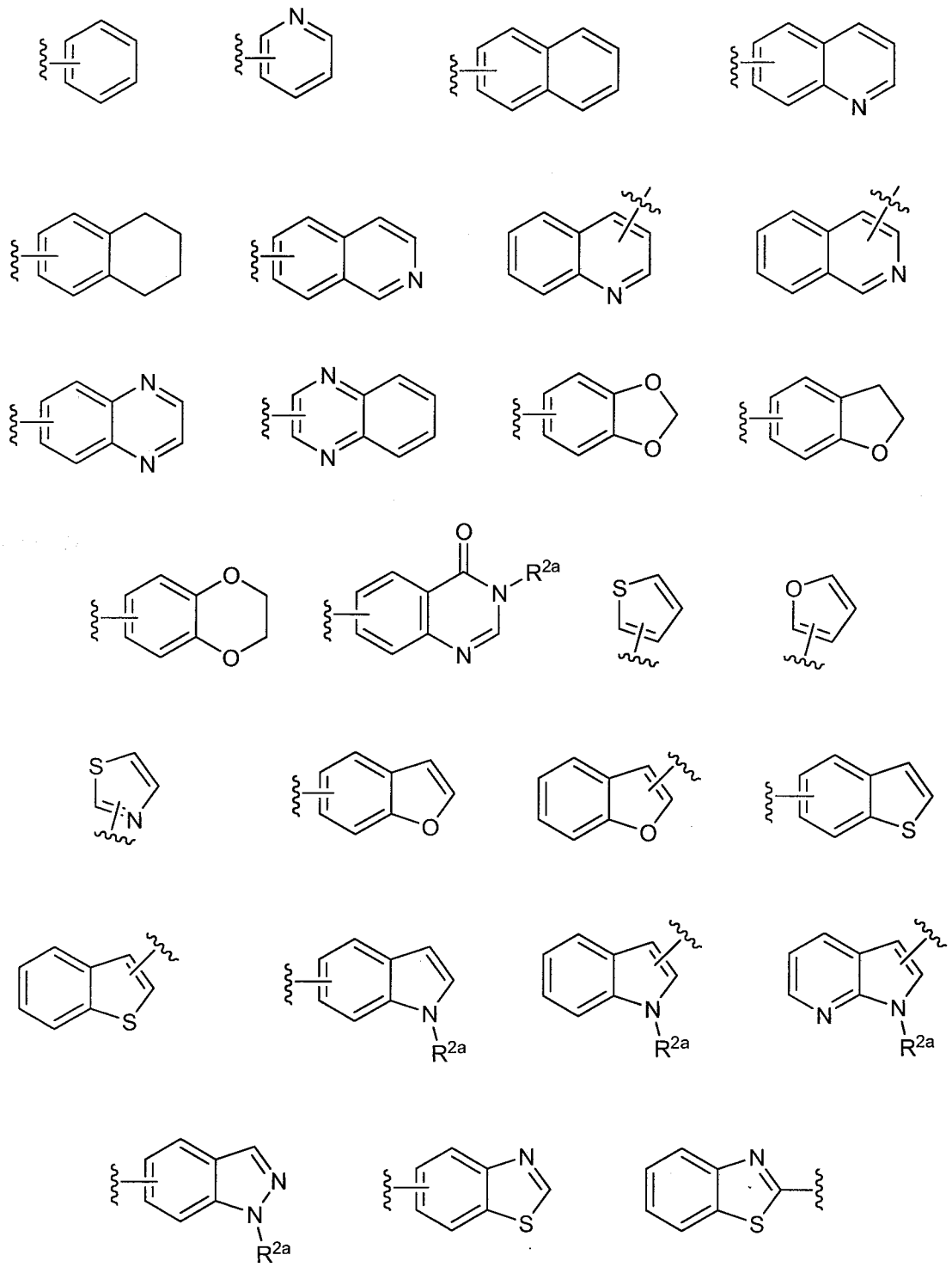


III

wherein G_1 is N or $-CR^8$, and R^8 is –CN; and wherein Ring A, n and R^2 are as defined for the compounds described generally and in subsets herein.

[00167] In certain embodiments, for compounds of general formula **III-i**, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

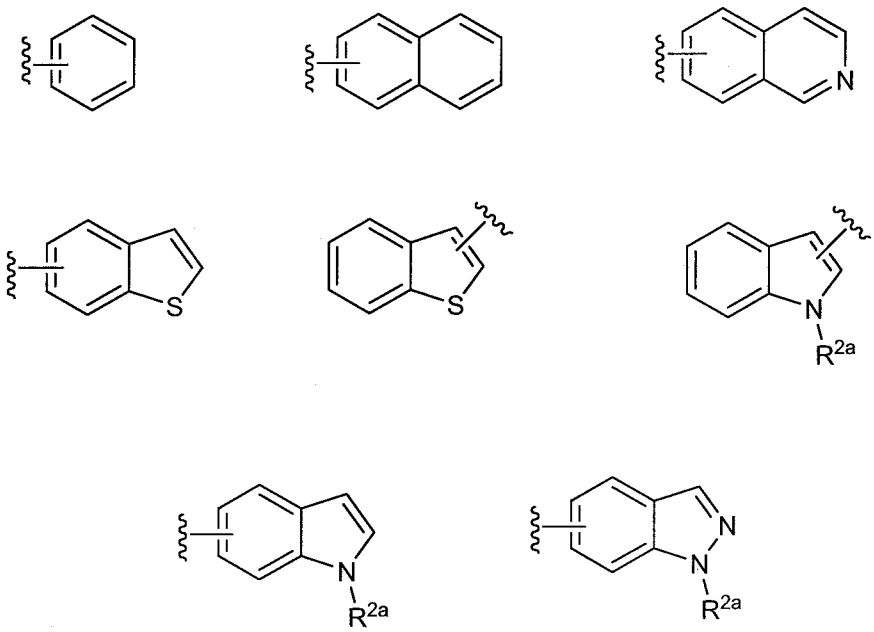
[00168] In other embodiments, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00169] In certain other embodiments, for compounds of general formula **III-i**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00170] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00171] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00172] In certain embodiments, for compounds of general formula **III-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl,

$-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00173] In certain embodiments, for compounds of general formula **III-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, or $-T_2-R^{12d}$, T_2 is an optionally substituted C_{1-6} alkylene chain, R^{12d} is $-N(R^{7b})_2$, and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

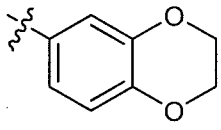
[00174] In certain embodiments, for compounds of general formula **III-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OC_{1-3}$ alkyl, or $-OC_{1-3}$ haloalkyl; and n is 0 to 3. In certain embodiments, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OCH_3$, or $-OCF_3$; and n is 0 to 3.

[00175] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00176] In still other embodiments, Ring A is a phenyl group, R^2 is halogen or $-(CH_2)N(R^{7b})_2$ and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 2.

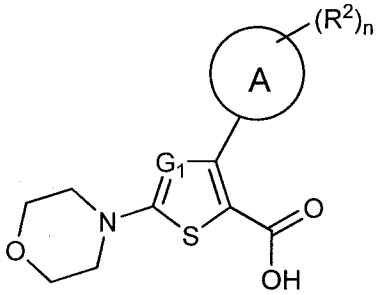
[00177] In certain embodiments, Ring A is a phenyl group, n is 1, and R^2 is in the para position. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the ortho and meta positions, and para with respect to each other.

[00178] In certain embodiments, Ring A is 2-chloro-5(dimethylaminomethyl)phenyl. In certain other embodiments, Ring A is 2-chloro-5(pyrrolidin-1-ylmethyl)phenyl.

[00179] In certain embodiments, for compounds of general formula **III-i**, Ring A is a 2-naphthyl group. In certain other embodiments, Ring A is .

[00180] In certain embodiments, for compounds of general formula **III-i**, Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring. In some embodiments, Ring A is substituted with one or more C_{1-3} alkyl groups.

[00181] In yet other embodiments, a compound having the structure of formula **IV-i** is provided:



IV-i

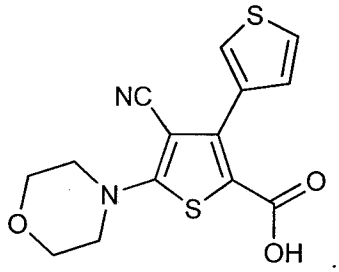
wherein Ring A, G_1, n and R^2 are as defined for compounds described generally above in subsets herein.

[00182] In certain embodiments, for compounds of general formula **IV-i**:

a) when G_1 is C-CN, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

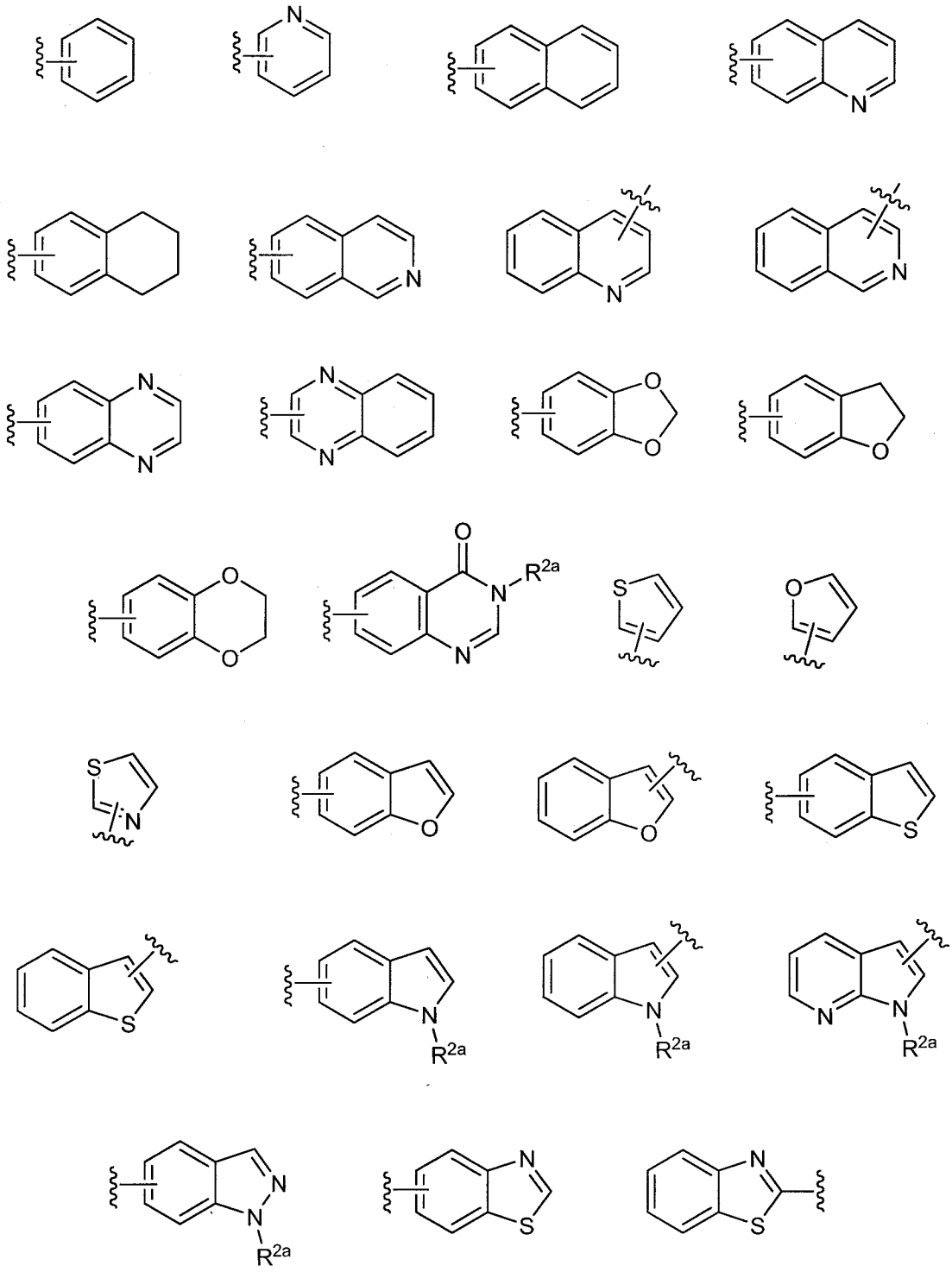
b) when G_1 is N, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

c) the compound is other than:



[00183] In certain embodiments, for compounds of general formula **IV-i**, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

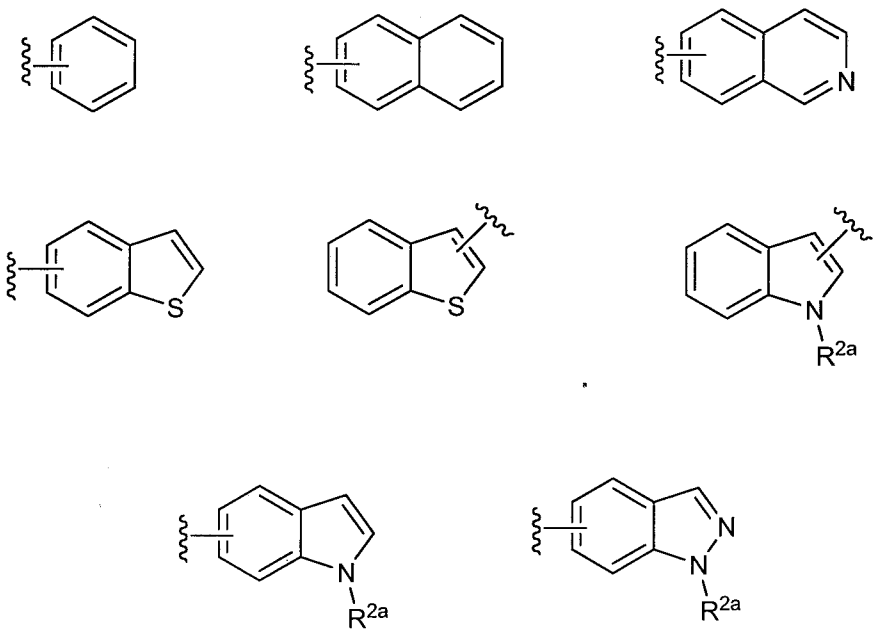
[00184] In other embodiments, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00185] In certain other embodiments, for compounds of general formula **VI-i**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00186] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00187] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00188] In certain embodiments, for compounds of general formula **IV-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl,

$-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or $-C(O)H$; and n is 0 to 3.

[00189] In certain embodiments, for compounds of general formula **IV-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, or $-T_2-R^{12d}$, T_2 is an optionally substituted C_{1-6} alkylene chain, R^{12d} is $-N(R^{7b})_2$, and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

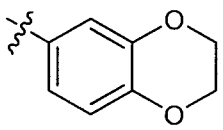
[00190] In certain embodiments, for compounds of general formula **IV-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OC_{1-3}$ alkyl, or $-OC_{1-3}$ haloalkyl; and n is 0 to 3. In certain embodiments, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OCH_3$, or $-OCF_3$; and n is 0 to 3.

[00191] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00192] In still other embodiments, Ring A is a phenyl group, R^2 is halogen or $-(CH_2)N(R^{7b})_2$ and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 2.

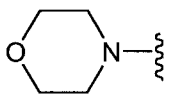
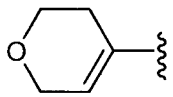
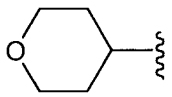
[00193] In certain embodiments, Ring A is a phenyl group, n is 1, and R^2 is in the para position. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the ortho and meta positions, and para with respect to each other.

[00194] In certain embodiments, Ring A is 2-chloro-5(dimethylaminomethyl)phenyl. In certain other embodiments, Ring A is 2-chloro-5(pyrrolidin-1-ylmethyl)phenyl.

[00195] In certain embodiments, for compounds of general formula **IV-i**, Ring A is a 2-naphthyl group. In certain other embodiments, Ring A is .

[00196] In certain embodiments, for compounds of general formula **IV-i**, Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring. In some embodiments, Ring A is substituted with one or more C_{1-3} alkyl groups.

[00197] In certain embodiments, for compounds of general formula **IA-i** or **IB-i**, HY is selected from:


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, and

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wherein each HY group is optionally additionally substituted with one or more occurrences of R^{14}.

[00198] In yet other embodiments, for compounds of general formula **IA-i** or **IB-i**, G_1 is N.

[00199] *4. Uses, Formulation and Administration*

[00200] As discussed above, the present invention provides compounds that are useful as inhibitors of PI3K enzymes, and thus the present compounds are useful for treating proliferative, inflammatory, or cardiovascular disorders such as tumor and/or cancerous cell growth mediated by PI3K. In particular, the compounds are useful in the treatment of cancers in a subject, including, but not limited to, lung and bronchus, prostate, breast, pancreas, colon and recum, thyroid, liver and intrahepatic bile duct, hepatocellular, gastric, glioma/glioblastoma, endometrial, melanoma, kidney, and renal pelvis, urinary bladder, utering corpus, uterine cervix, ovary, multiple myeloma, esophagus, acute myelogenous leukemia, chronic myelogenous leukemia, lymphocytic leukemia, myeloid leukemia, brain, oral cavity, and pharynx, small intestine, non-Hodgkin lymphoma, and villous colon adenoma.

[00201] In some embodiments, compounds of the invention are suitable for the treatment of breast cancer, bladder cancer, colon cancer, glioma, glioblastoma, lung cancer, hepatocellular cancer, gastric cancer, melanoma, thyroid cancer, endometrial cancer, renal cancer, cervical cancer, pancreatic cancer, esophageal cancer, prostate cancer, brain cancer, or ovarian cancer.

[00202] In other embodiments, compounds of the invention are suitable for the treatment of inflammatory and cardiovascular disorders including, but not limited to, allergies/anaphylaxis, acute and chronic inflammation, rheumatoid arthritis; autoimmunity disorders, thrombosis, hypertension, cardiac hypertrophy, and heart failure.

[00203] Accordingly, in another aspect of the present invention, pharmaceutical compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00204] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00205] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of PI3K.

[00206] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically

acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00207] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00208] In yet another aspect, a method for treating a proliferative, inflammatory, or cardiovascular disorder is provided comprising administering an effective amount of a compound, or a pharmaceutical composition to a subject in need thereof. In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutical composition is that amount effective for treating a

proliferative, inflammatory, or cardiovascular disorder, or is that amount effective for treating cancer. In other embodiments, an "effective amount" of a compound is an amount which inhibits binding of PI3K and thereby blocks the resulting signaling cascades that lead to the abnormal activity of growth factors, receptor tyrosine kinases, protein serine/threonine kinases, G protein coupled receptors and phospholipid kinases and phosphatases.

[00209] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating the disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disease being treated and the severity of the disease; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00210] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00211] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and

sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00212] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00213] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00214] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00215] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00216] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a)

fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00217] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00218] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00219] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are

also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00220] While one or more of the inventive compounds may be used in an application of monotherapy to treat a disorder, disease or symptom, they also may be used in combination therapy, in which the use of an inventive compound or composition (therapeutic agent) is combined with the use of one or more other therapeutic agents for treating the same and/or other types of disorders, symptoms and diseases. Combination therapy includes administration of the therapeutic agents concurrently or sequentially. Alternatively, the therapeutic agents can be combined into one composition which is administered to the patient.

[00221] In one embodiment, the compounds of this invention are used in combination with other therapeutic agents, such as other inhibitors of PI3K or other inhibitors such as mTor. In some embodiments, a compound of the invention is administered in conjunction with a therapeutic agent selected from the group consisting of cytotoxic agents, radiotherapy, and immunotherapy. It is understood that other combinations may be undertaken while remaining within the scope of the invention.

[00222] Another aspect of the invention relates to inhibiting PI3K, activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula I or a composition comprising said compound. The term "biological sample", as used herein, generally includes in vivo, in vitro, and ex vivo materials, and also includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00223] Still another aspect of this invention is to provide a kit comprising separate containers in a single package, wherein the inventive pharmaceutical compounds, compositions and/or salts thereof are used in combination with pharmaceutically acceptable carriers to treat disorders, symptoms and diseases where PI3K kinase plays a role.

EXPERIMENTAL PROCEDURES

[00224] **I-A. PREPARATION OF CERTAIN EXEMPLARY COMPOUNDS:** Compounds 1 through 92 (Shown in Table 1 below) were prepared using the general methods and specific examples described directly below.

[00225] 1. General Synthetic Methods and Intermediates:

[00226] The compounds of the present invention can be prepared by methods known to one of ordinary skill in the art and / or by reference to the schemes shown below and the synthetic examples that follow. Exemplary synthetic routes are set forth in Schemes 1-52 below, and in the Examples.

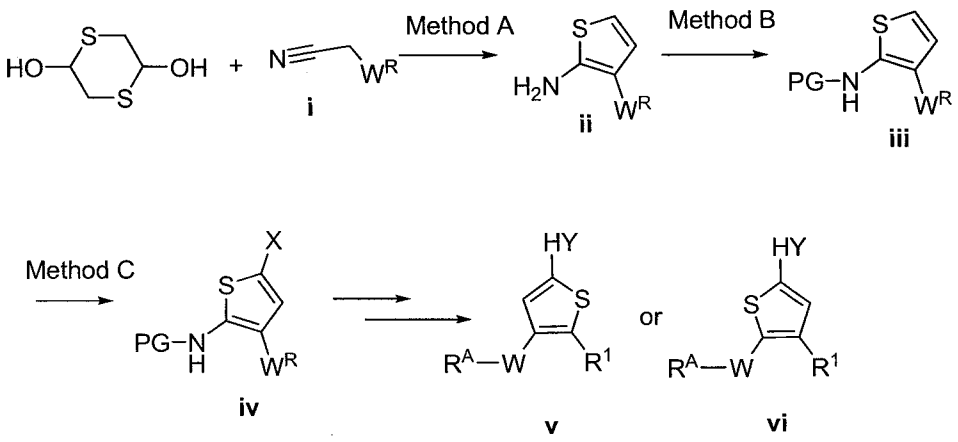
[00227] In methods defined below X represents halogen (Br, I or Cl), P is HY itself or a substituent convertible to HY by applying a generally known method, R^A represents Ring A, W^R is W-R^A itself, or a substituent convertible to W-R^A by applying a generally known method, W^L is R^A itself, or a part of W linker connected to R^A and Q is R^1 itself or a substituent convertible to R^1 by applying a generally known method.

[00228] Examples of the solvent for the below-mentioned reactions include, but are not limited to halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, aromatic hydrocarbons such as benzene, toluene, xylene and the like, alcohols such as methanol, ethanol, isopropanol, tert-butanol, phenol and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, DME and the like, acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like.

[00229] One of ordinary skill in the art will recognise that numerous variations in reaction conditions including variations in solvent, reagents, catalysts, reaction temperatures and times are possible for each of the reactions described. Variation of order of synthetic steps and alternative synthetic routes are also possible.

[00230] In many cases, synthesis can be started from commercially available thiophene / thiazole analogs to prepare target compounds. In some cases, specially functionalized thiophene / thiazole analogs can be prepared by the procedures described in Schemes 1-4.

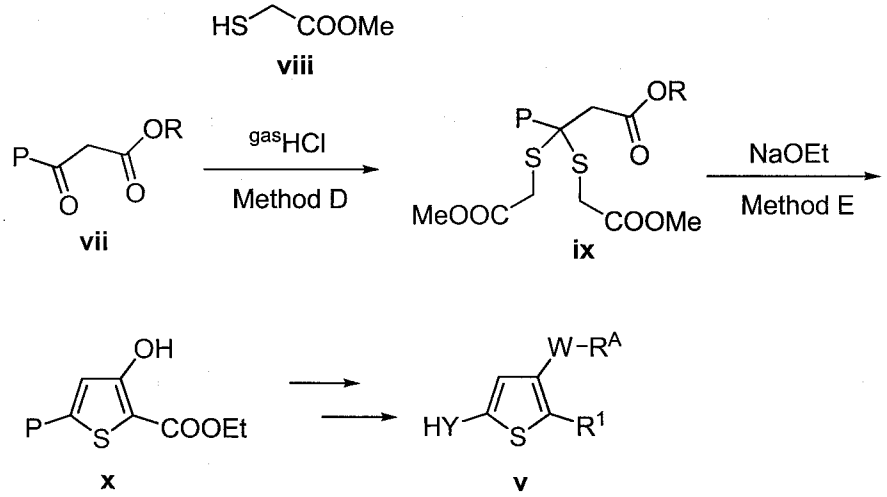
[00231] **Scheme 1: General method for the synthesis of 2-aminothiophenes**



[00232] Scheme 1 shows a procedure to prepare compounds of formula **v**.
Condensation of nitriles **i** with 2,5-dihydroxy-1,4-dithiane can be accomplished using reported procedure (C. E. Stephens et al. Bioorg. Med. Chem., 2001, 9, 1123-1132, Method A). Aminothiophenes **ii** may then be protected with an appropriate protecting group, for example Boc using standard conditions, such as Boc anhydride, DMAP, dioxane (Method B). Halogenation of protected thiophenes **iii** may be achieved using a suitable reagent, for example NBS in DCM to afford halides of formula **iv** (Method C), that can be converted into compounds of formula **v** by a combination of generally known functional group conversion reactions described below.

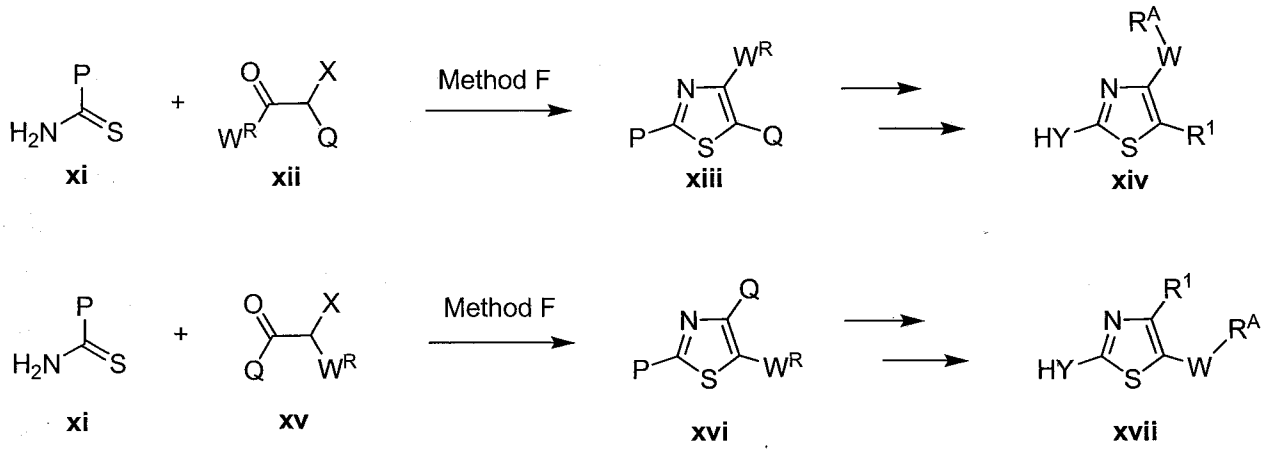
[00233] Alternatively, reverse type of thiophene analogs **vi** can also be prepared using functional group transformations described below.

[00234] **Scheme 2: General method for the synthesis of 4-hydroxyl thiophenes**



[00235] Suitably functionalized 4-hydroxyl thiophenes can be prepared according to the published procedure such as M. D. Mullican, et al., J. Med. Chem., 1991, 34, 2186—2194.
For example, scheme 2 describes a general procedure for preparing 4-hydroxythiophenes of formula **x**. Beta-ketoesters **vii** may be treated with thiols, such as methyl thioglycolate **viii** in the presence of suitable acid, such as HCl in ethanol (Method D), to afford dithio-ketal **ix**, which may then be treated with an appropriate base, like sodium ethoxide in a suitable solvent, for example, ethanol, to give 4-hydroxythiophenes of formula **x** (Method E). These 4-hydroxythiophenes can be converted to target compounds **v** according to the procedures described below.

[00236] **Scheme 3: General method for the synthesis of substituted thiazoles**

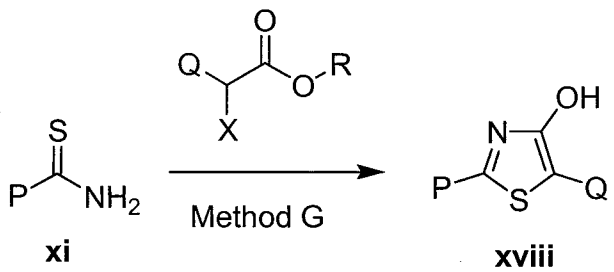


xi xii xiii xiv

xi xv xvi xvii

[00237] Scheme 3 shows a general route for the synthesis of compounds of formula **xiii** and **xvi**. Thioamides **xi** or thioureas (When P = NHR) may be treated with alpha-halogenated carbonyl compounds **xii** in a suitable solvent, such as isopropanol at elevated temprerature to give thiazoles **xiii**. (Method F). When P = NH_2, 2-aminothiazoles **xiii** that are obtained can be then subjected to Sandmeyer reaction to afford 2-halothiazoles **xxxi** (P = X), which can be used for further functional transformations described below. A conversion reaction from **xiii** to compounds **xiv** can be performed, for example, by a combination of generally known functional group conversion reactions shown below.
If an alpha-halogenated carbonyl compound is suitably selected, i.e. **xv**, reverse type thiazole analogs **xvi** and **xvii** can be also prepared using well known organic functional group transformation reactions described below.

[00238] **Scheme 4: General method for the preparation of 4-hydroxythiazoles**



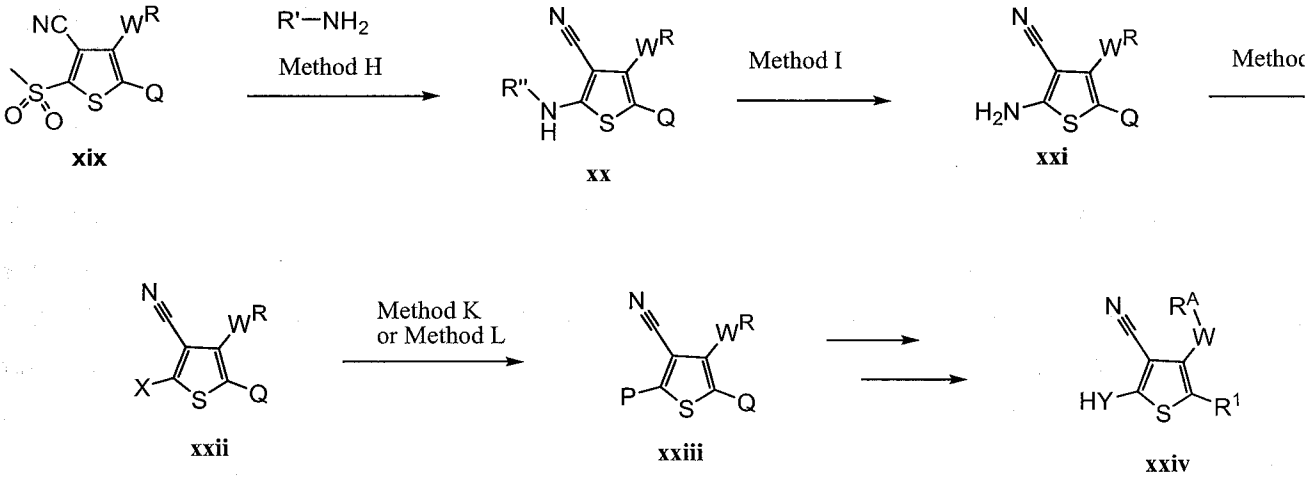
xi xviii

As shown in scheme 4, thioamides **xi** can be condensed with alpha-halogenated esters in a similar manner as reported by Rzasa, R.M. et al, Bioorg. Med. Chem. **2007,** *15*, 6574 to obtain 4- hydroxythiazole derivatives **xviii**. The reaction can be carried out in a suitable solvent, such as ethanol, in the presence of an appropriate base, *i.e.*, pyridine, under elevated temperature (Method G).

[00239] Schemes 5-19 describe procedures for basic functional group transformations on thiophene / thiazole central core scaffolds.

[00240] In the schemes 5-8, general functional group transformation procedures for introduction of the HY group are described.

[00241] Scheme 5: Introduction of HY to 3-cyanothiophenes



[00242] Scheme 5 describes the procedure for the introduction of HY to 3-cyanothiophene analogs by a known functional group transformation reaction.

As shown in Scheme 5, sulfones of formula **xix** (synthetic examples given in Mansanet et al, WO 2005070916) may be treated with amines R'-NH_2, such as 2,4-dimethoxybenzylamine, in a suitable solvent, *e.g.*, THF, at elevated temperature (Method H) to give **xx**.

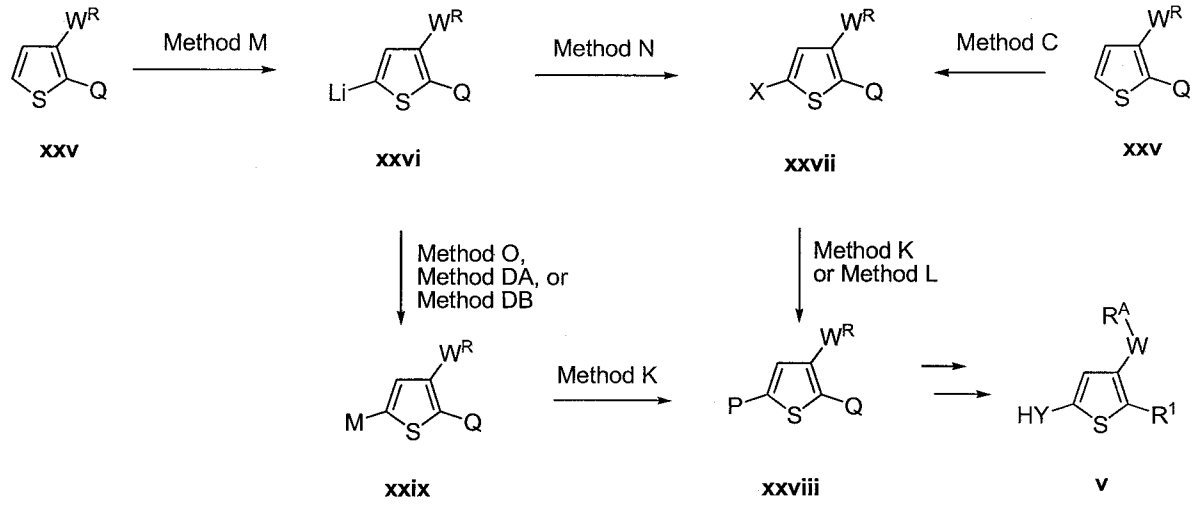
Deprotection of R'' group may be carried out using a standard procedure, in the case of dimethoxybenzyl group with an acid, such as TFA in DCM, to afford amines **xxi** (Method I).

Amines **xxi** can then be subjected to Sandmeyer reaction using appropriate reagents, such as methylene iodide and amyl nitrite in ACN (Method J).

The resulting halogenated thiophenes **xxii** can be coupled with aryl stannanes under suitable conditions, for example $Pd(PPh_3)_4$, CuI, LiCl in a suitable solvent, such as dioxane, at elevated temperature to give compounds of formula **xxiii** (Method K). Alternatively, boronic acids or esters can be used for such coupling reactions, for example $Pd(PPh_3)_4$, Na_2CO_3, DME/water, elevated temperature or microwave irradiation (Method L).

A conversion reaction from **xxiii** to compounds **xxiv** can be performed, for example, by a combination of generally known functional group conversion reactions shown below.

[00243] Scheme 6: General method for the introduction of HY to 2-unsubstituted thiophenes.



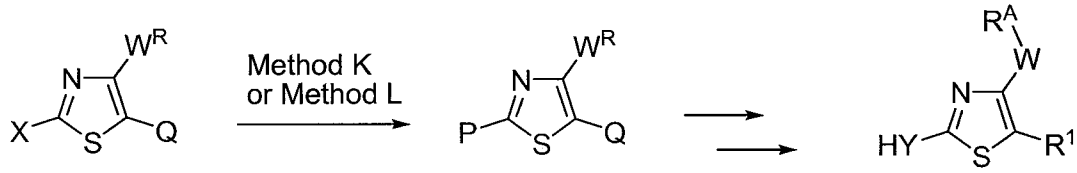
[00244] Scheme 6 shows a general route for introducing HY to unsubstituted 2-position of thiophene core.

2-unsubstituted thiophenes **xxv** can be treated with suitable base, such as n-BuLi in THF at low temperature, to produce lithiated thiophene intermediates **xxvi** (Method M). The intermediate organolithium species can be quenched with halogen molecule, for example iodine in a suitable solvent, such as THF, to afford halogenated compounds of formula **xxvii** (Method N). Alternatively, thiophenes **xxv** can be directly halogenated using suitable conditions, for example NBS in DCM to afford halogenated compounds of formula **xxvii** (Method C). Halides **xxvii** can be coupled with aryl stannanes under suitable conditions, for example $Pd(PPh_3)_4$, CuI, LiCl in a suitable solvent, such as dioxane at elevated temperature to give compounds of formula **xxviii** (Method K), or boronic acids or esters. with an appropriate catalyst, for example $Pd(PPh_3)_4$, in the presence of a suitable base, such as sodium carbonate, in DME-water mixture at elevated temperature (Method L) to afford compounds of formula **xxviii**. Alternatively, lithium intermediates **xxvi** can be transformed to organometallic reagents, such as stannanes by quenching with suitable tin halide, such as tributyltin chloride (Method O), or boronic esters, such as alkoxy-tetramethyl-1,3,2-dioxaborolane (method DA), or trifluoroborates by the subsequent treatment of boronic esters with a suitable fluorine source, such as KHF_2 (Method DB). Stannanes **xxix** may then be coupled with aryl halides, triflates, or mesylates using appropriate conditions, such as $Pd(PPh_3)_4$, CuI, LiCl in a suitable solvent, such as dioxane, at elevated temperature to give compounds of formula **xxviii** (Method K). Boronic acids, esters or trifluoroborates can be then coupled with aryl halides, triflates, or mesylates with an appropriate catalyst, for example $Pd(PPh_3)_4$, in the presence of a suitable base, such as sodium carbonate in DME-water mixture at elevated temperature

(Method L) to afford compounds of formula **xxviii**.

A conversion reaction from **xxviii** to compounds **v** can be performed, for example, by a combination of generally known functional group conversion reactions shown below.

[00245] Scheme 7: General method for introduction of HY to 2-position of thiazole core.

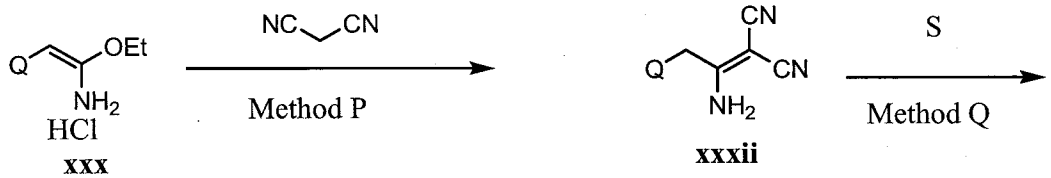


xxxi **xiii** **xiv**

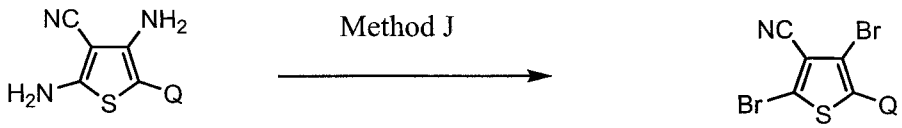
[00246] Scheme 7 shows a general route for introducing HY to 2-position of thiazole core scaffold. Halogenated thiazoles **xxxi**, which may be available as described in scheme 3, can coupled with suitable partners, such as boronic acids, stannanes, etc under standard Suzuki conditions, such as $Pd(PPh_3)_4$, Na_2CO_3, DME/water, elevated temperature or microwave irradiation (Method L), or standard Stille conditions, such as $Pd(PPh_3)_4$, CuI, LiCl, dioxane at elevated temperature (Method K) to afford compounds of formula **xiii**.

A conversion reaction from **xiii** to compounds **xiv** can be performed, for example, by a combination of generally known functional group conversion reactions shown below.

[00247] Scheme 8: General method for the synthesis of 3-cyanothiophenes



xxx **xxxii**



xxxiii **xxxiv**

[00248] Scheme 8 describes the procedure for the synthesis of 3-cyanothiophenes **xxxiv**. Substituted alkoxyethenamine **xxx** may be treated with malononitrile in the presence of a suitable base, such as TEA, in a suitable solvent, like chloroform, at elevated temperature to afford substituted aminoethylene malononitriles **xxxii** (Method P), that are treated with sulfur under suitable conditions, such as DMF and elevated temperature, to give diaminocyanothiophenes **xxxiii** (Method Q). Diamines **xxxiii** may then be subjected to a Sandmeyer reaction using appropriate reagents, such as copper(II)bromide, amyl nitrite in ACN at elevated temperature (Method J) to afford compounds of formula **xxxiv**.

[00249] Schemes 9—21 describe methods for the introduction of R^1 and W-R^A groups.

[00250] **Scheme 9: General method for the synthesis of preparation of 4-alkoxy thiophene / thiazole derivatives.**

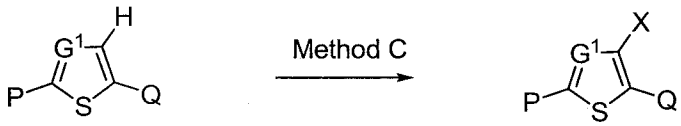


xviii **xxxv**

4-Alkoxy thiophenes/ thiazoles can be obtained by the conventional alkylation method of 4-hydroxythiazole derivatives obtained in scheme 4.

As shown in scheme 9, 4-hydroxy thiophenes / thiazoles **xviii** can be treated with alkyl halides using a suitable base, such as potassium carbonate, in a suitable solvent, for example DMF, at elevated temperature to afford compounds of formula **xxxv** (Method R).

[00251] **Scheme 10: General method for halogenation of thiophenes / thiazoles**



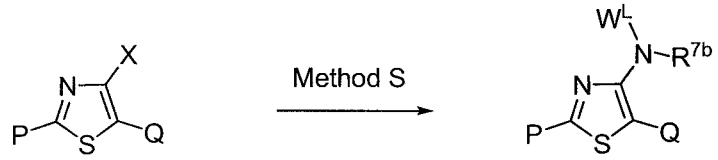
xxxvi **xxxvii**

[00252] Scheme 10 shows a general route for introducing halogen functionality at the 4-unsubstituted position of thiophene / thiazole core.

Halogenation of thiophene / thiazoles can be achieved in a similar manner as reported in the literature (Takami et al, Tetrahedron **2004**, *60*, 6155). For example, **xxxvi** is treated with a generally known halogenating reagent, such as bromine or N-bromosuccinimide, in a suitable solvent, such as DCM, at elevated temperature to afford compounds of formula **xxxvii** (Method C).

The halogenated thiazole **xxxvii** can be used for further functional group transformation shown below.

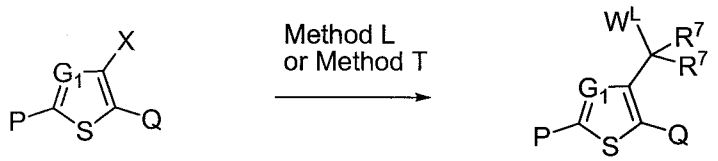
[00253] **Scheme 11: General method for the preparation of 4-aminothiazoles**



xxxviii **xxxix**

[00254] Scheme 11 shows general methods for the synthesis of 4-aminothiazole derivatives **xxxix** from 4-halogenated thiazoles **xxxviii**, which can be prepared by the procedure described in scheme 10. Displacement of a halogen group with an amine can be achieved in a similar manner as reported in the literature (J. Med. Chem **2006**, *49*, 5769). Treatment of **xxxviii** with an amine at elevated temperature in a suitable solvent, such as DMF, can lead to amines **xxxix** (Method S). If necessary a base, such as sodium carbonate, can be added.

[00255] Scheme 12: General method for introducing carbon functionality to 4-halogenated thiophenes / thiazoles.

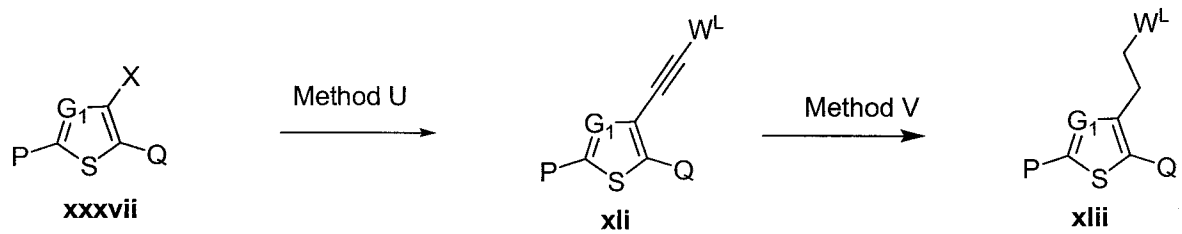


xxxvii **xv**

[00256] As shown in Scheme 12, carbon functionality can be introduced by the well known cross-coupling technique from the 4-halogenated thiophenes / thiazoles **xxxvii** which can be prepared by the procedure described in scheme 10.

For example, **xv** can be obtained from 4-halogenated thiophenes / thiazoles **xxxvii** by reaction with an organic boronic acid reagent, or an organic zinc reagent in a presence of palladium catalyst. Suzuki couplings with alkyl, alkenyl boronic acids or esters can be performed using $Pd(PPh_3)_4$, or a similar palladium catalyst, a suitable base, such as sodium carbonate in an appropriate solvent, such as DME/water, at elevated temperature (Method L), while $Pd(tBu_3P)_2$ can be used for Negishi coupling reactions, together with in a suitable solvent, such as THF, at elevated temperature (Method T).

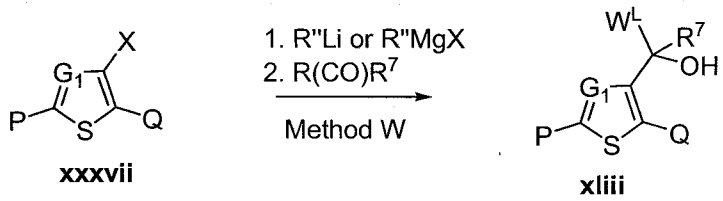
[00257] Scheme 13: General method for introducing carbon functionality to 4-halogenated thiophenes / thiazoles.



xxxvii **xli** **xlii**

[00258] Scheme 13 shows a general method for the synthesis carbon substituted thiophenes/thiazoles. 4-halogenated thiophenes/thiazoles **xxxvii** can be treated with an alkyne in the presence of a suitable catalyst, for example $Pd(PPh_3)_4$, CuI, base, such as TEA in a suitable solvent, like DCM, to afford alkynes **xli** (Method U). Compounds **xli** can be then reduced to alkyl substituted thiophenes/thiazoles **xlii**, for example using hydrogenation with Pd/C in a suitable solvent, such as ethanol (Method V)

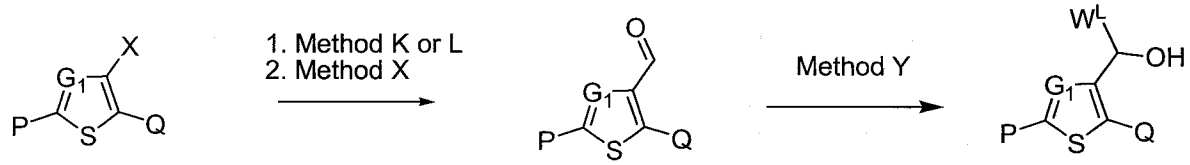
[00259] **Scheme 14: General method for introducing carbon functionality to halogenated thiophenes.**



xxxvii **xliii**

[00260] Scheme 14 shows a general method for the synthesis of carbon substituted thiophenes. Halogenated thiophenes **xxxvii** can be treated with alkyllithium, arryllithium or alkylmagnesium reagents, such as of *n*-BuLi at low temperature to generate intermediate metallated thiophenes that are subsequently treated with aldehydes or ketones to afford carbinols **xliii** (Method W).

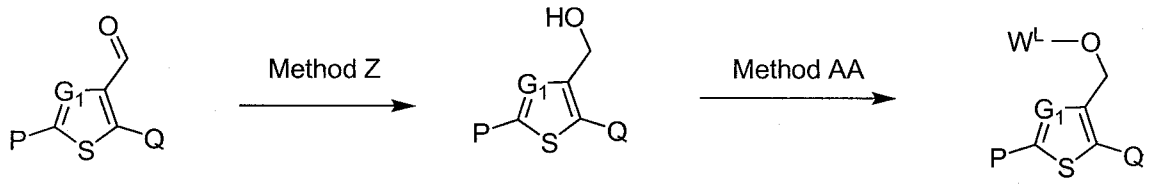
[00261] **Scheme 15: General method for introducing carbon functionality to 4-halogenated thiophenes / thiazoles.**



xxxvii **xliv** **xlv**

[00262] Scheme 15 shows a general method for the synthesis carbon substituted thiophenes/thiazoles. Halogenated thiophenes/thiazoles **xxxvii** can be treated with vinylorganometallic reagents, for example vinyltributylstannane under Stille conditions (Method K), or vinyltrifluoroborate under Suzuki conditions (Method L) to afford vinyl thiophenes/thiazoles, that can be oxidized to aldehydes **xliv** using a suitable method, for example OsO_4, sodium periodate in water-dioxane mixture (Method X). Aldehydes **xliv** can be then treated with organometallic reagents, such as Grignard or alkyl/aryllithium compounds in a suitable solvent, such as THF, at low temperature to afford carbinols of formula **xlv** (Method Y).

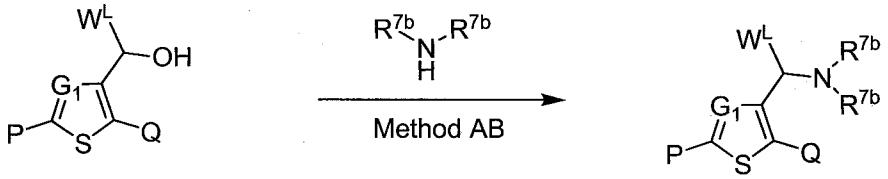
[00263] **Scheme 16: General method for the synthesis of ethers**



xliv **xlvi** **xlvii**

[00264] Scheme 16 shows a general method for the synthesis of alcohols **xlvi** and ethers **xlvii**. Aldehydes prepared as described in Scheme 15 above can be treated with a suitable reducing agent, such as $NaBH_4$ in an appropriate solvent, for example THF, to afford alcohols of formula **xlvi** (Method Z). Alcohols **xlvi** can be then alkylated using standard conditions, for example with alkyl halides in the presence of base, such as K_2CO_3, in THF to afford ethers **xlvii** (Method AA).

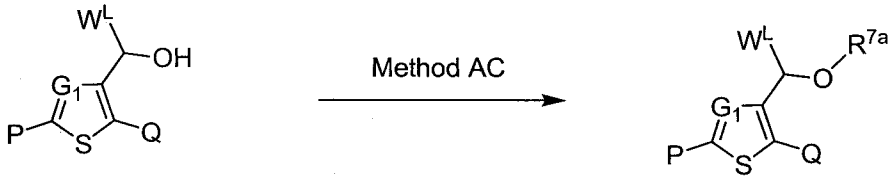
[00265] **Scheme 17: General method for the synthesis of amines**



xlv **xlviii**

[00266] Scheme 17 shows a general method for the synthesis of amines **xlviii**. As shown is Scheme 17, alcohols can be activated via sulfonyl esters, for example by reaction with methanesulfonic chloride and a base, such as pyridine in a suitable solvent, for example DCM. Sulfonyl esters are then treated with amines at elevated temperature to provide target amines **xlviii** (Method AB).

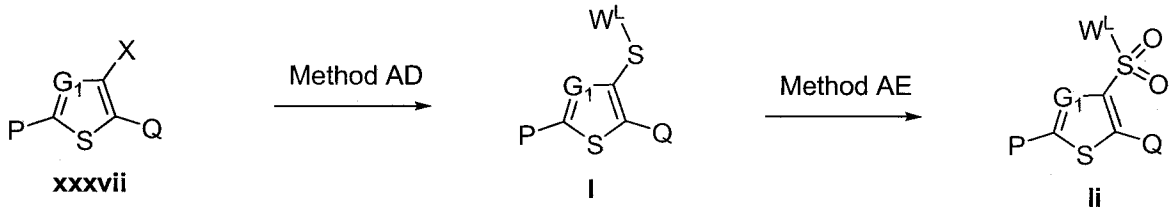
[00267] **Scheme 18: General method for the synthesis of ethers**



xlv **il**

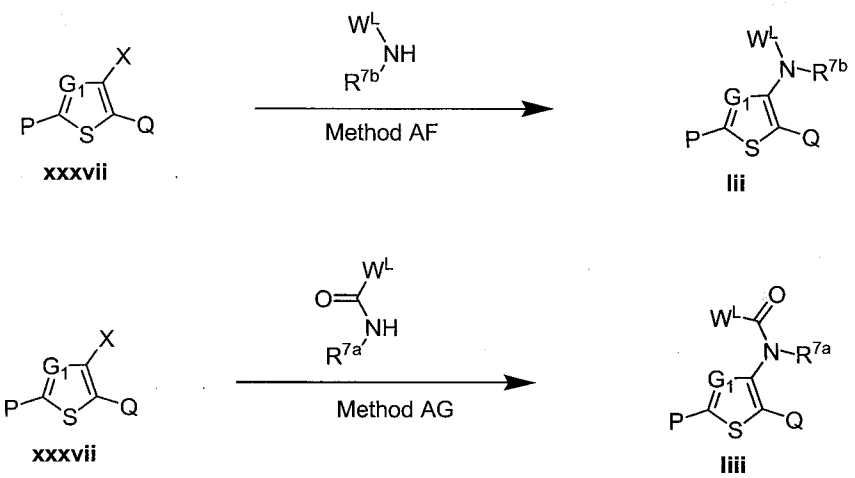
[00268] Scheme 18 shows a general method for the synthesis of ethers **il** when W^L is an aromatic or heteroaromatic group. As shown is Scheme 18, alcohols **xlv** are treated with an excess of alcohol, such as methanol, in the presence of an acid, like aqueous HCl with an optional co-solvent, for example dioxane at ambient temperature to afford ethers of formula **il**.

[00269] **Scheme 19: General method for introducing sulfur functionality**



[00270] As shown in Scheme 19, sulfur functionality can be introduced to the 4- halogenated thiazoles/thiophenes **xxxvii** by a similar manner as described by Rossignol et al, US2009036467. Treatment of **xxxvii** with thiols in the presence of a copper catalyst, like CuI in a suitable solvent, such as DMF, with an appropriate base, for example sodium hydroxide, at elevated temperature gives thioethers of formula **I** (Method AD). Thioethers **I** can subsequently be oxidized to sulfones **Ii** using a suitable oxidating agent, for example mCPBA in DCM (Method AE).

[00271] **Scheme 20: General method for Pd-catalyzed amination /amidation of 4-halogenated thiophenes / thiazoles**

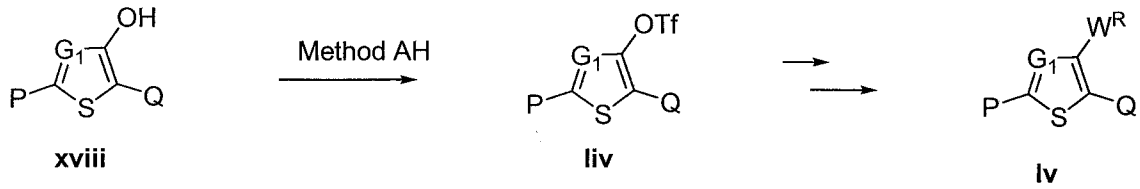


[00272] As shown in Scheme 20, amine or amide functionality can be introduced by the well known palladium catalyzed amination / amidation reaction, so called Buchwald coupling, to the 4-halogenated thiophenes / thiazoles **xxxvii**.

For example, halides **xxxvii** can be treated with amines using an appropriate Pd catalyst, such as Pd_2dba_3/BINAP, with a suitable solvent/base combination, for example NaOtBu in toluene at elevated temperature or using microwave irradiation to afford amines of formula **Iii** (Method AF).

Coupling with amides also can be carried out using a suitable Pd catalyst, for example Pd_2dba_3/XantPhos, with a suitable solvent/base combination, like Cs_2CO_3 in dioxane at elevated temperature or using microwave irradiation to give amides of formula **Iiii** (Method AG).

[00273] **Scheme 21: General method for the functionalization of 4-hydroxyl group of thiophene / thiazole derivatives**

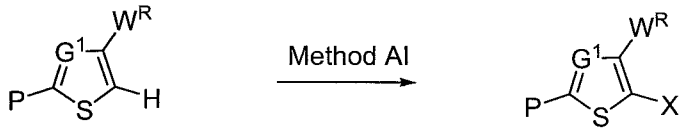


xviii liv lv

[00274] As shown in Scheme 21, 4-hydroxythiazoles or thiophenes **xviii** can be transformed to various functionalized thiazole / thiophene derivatives via triflate **liv**.

For example, compounds **xviii** can be transformed into triflates **liv**, using, *e.g.*, triflic anhydride, with pyridine as base in DCM (Method U). Triflates **liv** can be then subjected to coupling reactions with amines, boronic esters, stannanes, or thiols under similar conditions as described for analogous halides in Schemes 11 – 14 (analogous literature examples include Rzasa, R. et al, Bioorg. Med. Chem. **2007**, *15*, 6574; Langille, N.F., Org. Lett. **2002**, *4*, 2485.) to afford compounds of formula **lv**.

[00275] **Scheme 22: General method for halogenation of 3-posittion onto thiophene / thiazoles.**



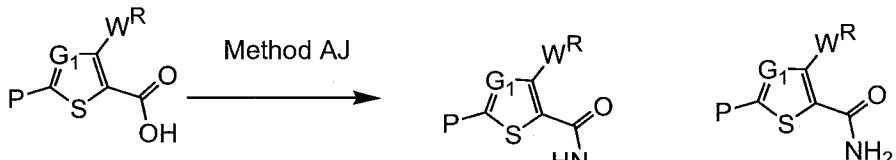
lvi lvii

[00276] Scheme 22 shows a general route for introducing halogen functionality onto unsubstituted 5-position of thiophene / thiazole core scaffold.

Halogenation of 5-unsubstituted thiazoles / thiophenes can be achieved in a similar manner as reported in the literature (Haelmmerle et al, Synlett **2007**, 2975). For example, **lvi** is treated with a generally known halogenating reagent such as bromine or N-bromosuccinimide in a suitable solvent, such as DCM to afford compounds of formula **lvii** (Method AI).

The resulting halogenated thiophenes / thiazoles **lvii** can be used for the further functional group transformation reaction such as described in scheme 11—15.

[00277] **Scheme 23: General route for the synthesis of carboxamides**



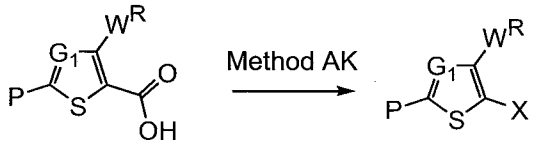
lviii lix lx

[00278] Scheme 23 shows a general route for preparing amide compounds of formula **lix**.

As shown in Scheme 23, acids **lviii** may be treated with amines using standard coupling conditions, such as EDCI and HOBt in DCM to afford amides **lix** (Method AJ).

When ammonia is used as an amine source, primary amide derivatives **lx** may be obtained, which can be used as intermediates for the construction of azoles as described in Schemes 25, 26, 28 and 37.

[00279] Scheme 24: General route for the synthesis of 5-halogenated thiophenes / thiazoles by Hunsdiecker reaction

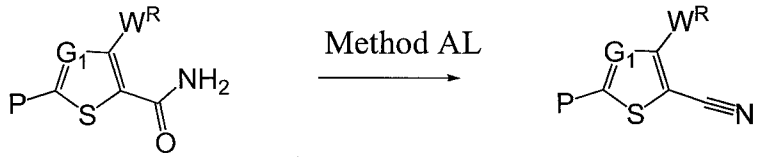


lviii **lvii**

[00280] As shown Scheme 24, 5-halogenated thiophenes / thiazoles **lvii** can be prepared by the Hunsdiecker reaction from thiophene /thiazole carboxylic acid analogs **lviii**.

As shown in Scheme 24, acids **xlviii** may be treated with sliver hydroxide to form a silver salt, which is subsequently treated with halogen, for example bromine, in a suitable solvent, such as CCl_4 at elevated temperature to form **lvii** (Method AK).

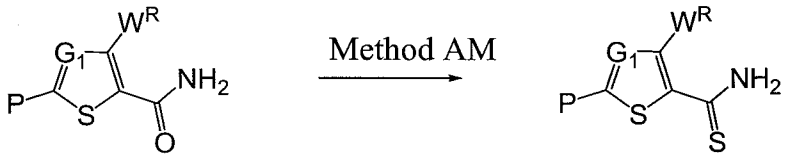
[00281] Scheme 25: General route for the synthesis of 5-cyano thiophenes / thiazoles



lx **lxiv**

[00282] As shown in scheme 25, amides **lx**, which can be prepared by the procedure described in scheme 23, are treated with phosphoryl chloride, or similar reagents to form 5-cyano thiophenes / thiazoles of formula **lxiv** (Method AL).

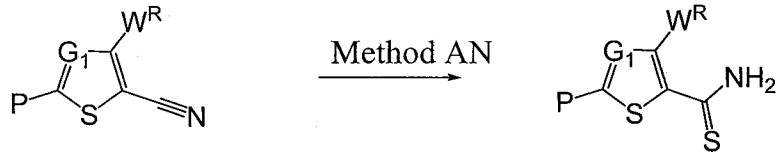
[00283] Scheme 26: General route for the synthesis of thioamides



lx **lxv**

[00284] As shown in scheme 26, amides **lx**, which can be prepared by the procedure described in scheme 23, are treated with a suitable reagent, for example Lawesson's reagent, or P_2S_5 in a suitable solvent, such as toluene at elevated temperature to afford thioamides of formula **lxv** (Method AM).

[00285] Scheme 27: Alternative route for the synthesis of thioamides



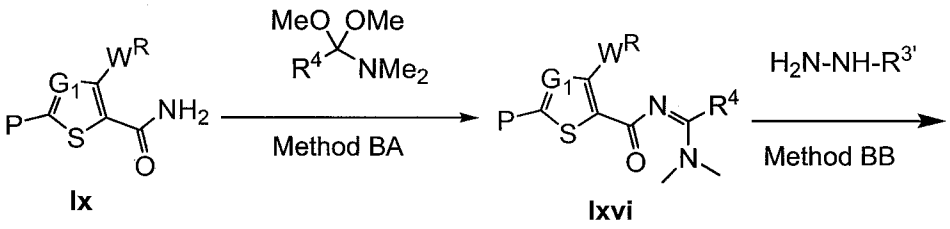
lxiv lxv

[00286] As shown in scheme 27, 5-cyano thiazoles / thiophenes **lxiv**, which can be prepared by the procedure described in scheme 25, are treated with a suitable reagent, for example ammonium sulfide in a suitable solvent, such as methanol to afford thioamides of formula **lxv** (method AN).

[00287] In the schemes 28—46, general procedures for the construction of the representative azoles as R^1 are described.

Schemes 28 -30 describe the formation of 1,2,4-triazolyl group as R^1.

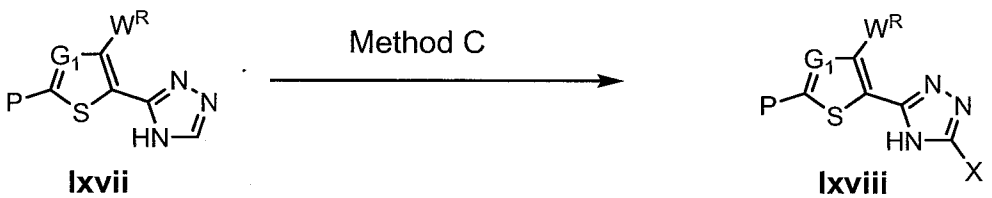
[00288] **Scheme 28: General route for the construction of 1,2,4- triazolyl**



lx lxvi lxvii' lxvii"

[00289] As shown in Scheme 28, amides **lx**, which can be prepared by the procedure described in scheme 23, can be treated with DMF-DMA at elevated temperature or under microwave irradiation (Method BA) to give intermediate amidines **lxvi** that are transformed to 1,2,4-triazoles **lxvii'** and **lxvii"** using hydrazine or substituted hydrazines in acetic acid at elevated temperature or under microwave irradiation (Method BB).

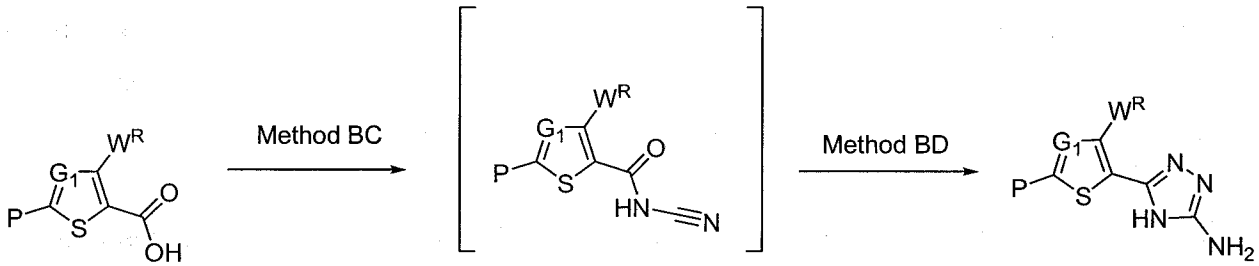
[00290] **Scheme 29: General route for the construction of 5-halogenated 1,2,4-triazolyl**



lxvii lxviii

[00291] As shown in Scheme 29, 1,2,4-triazoles **lxvii**, which can be prepared by the procedure described in scheme 28, are treated with a suitable halogenating agent, like NBS, in a suitable solvent, for example tetrachloromethane, to afford compounds of formula **lxviii** (Method C).

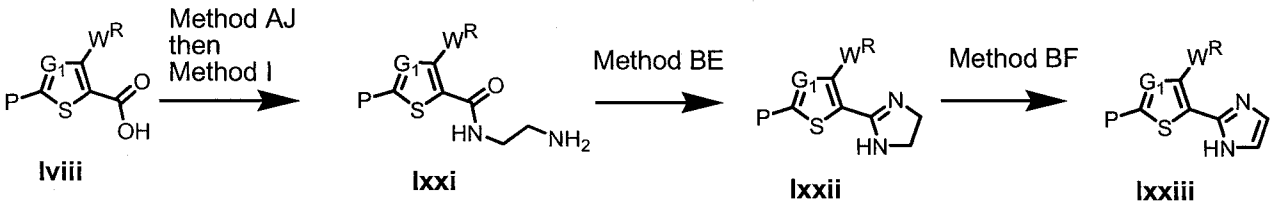
[00292] **Scheme 30: General route for the construction of 5-amino-1,2,4-triazolyl**



[00293] As shown in Scheme 30, acids **lviii** may be coupled with cyanamide, for example via an intermediate acid halide in a suitable solvent, such as DCM to acylcyanamides **lxix** (Method BC), that are in turn treated with hydrazine using appropriate conditions, for example acetic acid at elevated temperature to give compounds of formula **lxx** (Method BD).

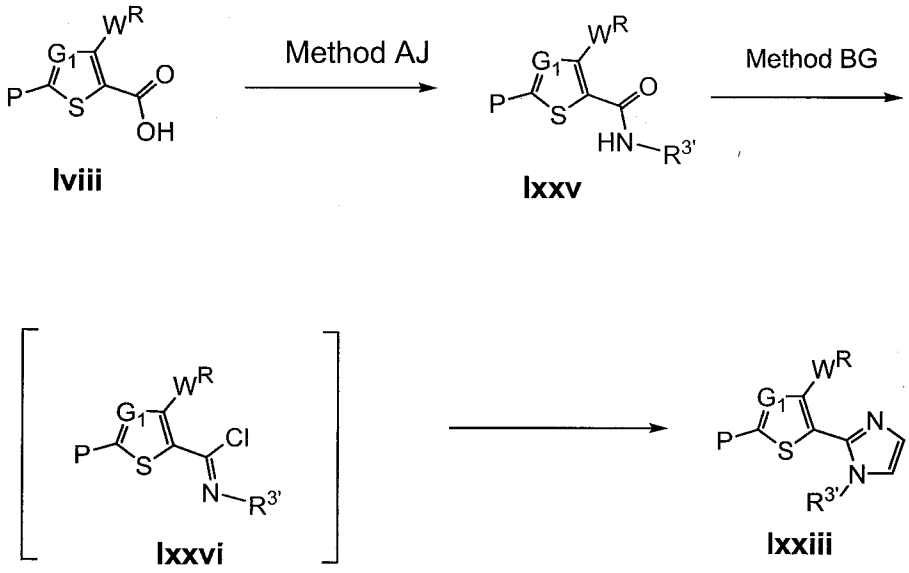
[00294] Scheme 31—39 describes the formation of 2-imidazolyl group as R^1.

[00295] **Scheme 31: General route for the construction of 2-imidazolyl**



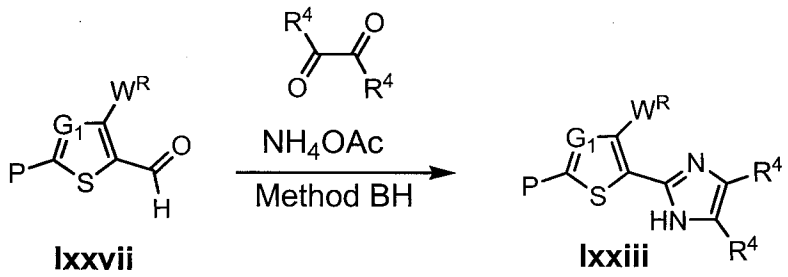
[00296] As shown in Scheme 31, acids **lviii** are treated with Boc protected ethylenediamine using standard coupling conditions, such as EDCI and HOBt in DCM (Method AJ). Protective group is removed using an appropriate acid, for example TFA in DCM to give amide **lxxi** (Method I). Cyclization of **lxxi** is achieved using suitable conditions, for example $POCl_3$ (Method BE) to form dihydroimidazoles **lxxii**. Dihydroimidazoles **lxxii** can be oxidized to imidazoles **lxxiii** using a suitable oxidative method, for example heating with Magtrieve (Method BF).

[00297] **Scheme 32: Alternative route for the construction of 2-imidazolyl**



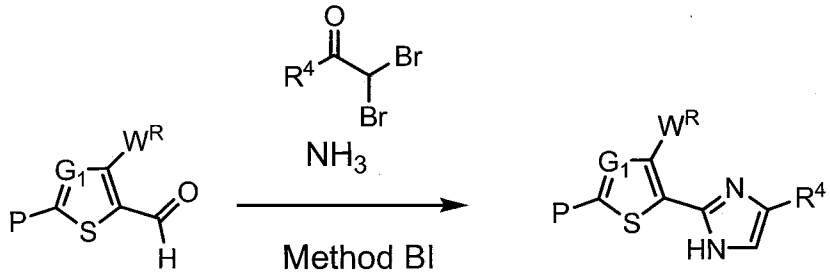
[00298] Scheme 32 above shows an alternative route for preparing imidazoles of formula **lxxiii**. As shown in Scheme 32, acids **lviii** are treated with amines using standard coupling conditions, such as EDCI and HOBt in DCM to afford amides **lxxv** (Method AJ). Cyclization to imidazoles may be achieved through a 3-step one pot process that involves treatment with phosphorus pentachloride and HCl in dioxane to afford carbimidoyl chloride intermediates **lxxvi**, that can be then treated with aminoacetaldehyde dimethylacetal followed by HCl in dioxane at elevated temperature to give **lxxiii** (Method BG). When $R^{3'}$ = allyl, benzyl or substituted benzyl, it can also serve as a protecting group.

[00299] **Scheme 33: Alternative route for the synthesis of 2-imidazolyl**



[00300] As shown in scheme 33, aldehydes **lxxvii** may be condensed with dicarbonyl compounds, such as diketones, ketoaldehydes, or glyoxal with an appropriate ammonia source, such as ammonium acetate, with suitable acid, such as acetic acid in solvent such as methanol to form imidazoles **lxxiii** (Method BH).

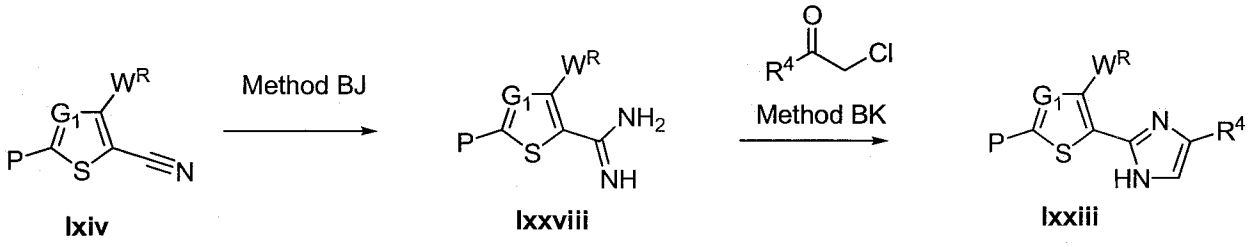
[00301] **Scheme 34: Alternative method for the construction of substituted 2-imidazolyl.**



lxxvii lxxiii

[00302] As shown in scheme 34, aldehydes of formula **lxxvii** can be treated with alpha, alpha-dihalo-ketones under suitable conditions, such as ammonium hydroxide, sodium acetate in an appropriate solvent, for example methanol and water to afford imidazoles of formula **lxxiii** (Method BI).

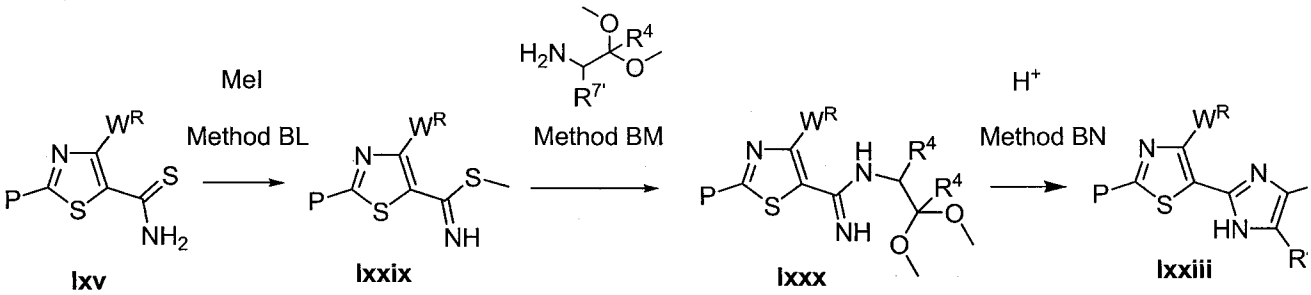
[00303] **Scheme 35: Alternative method for the construction of substituted 2-imidazolyl.**



lxiv lxxviii lxxiii

[00304] As shown in scheme 35, treatment of nitriles **lxiv**, which can be prepared by the procedure described in scheme 25, with LiHMDS in a suitable solvent mixture, such as THF/ether/hexane gives amidines of formula **lxxviii** (Method BJ) that can be treated with haloketones in the presence of a suitable base, such as potassium carbonate in an appropriate solvent, such as DCM under elevated temperature to give imidazoles of general formula **lxxiii** (Method BK).

[00305] **Scheme 36: Alternative method for the construction of substituted 2-imidazolyl.**

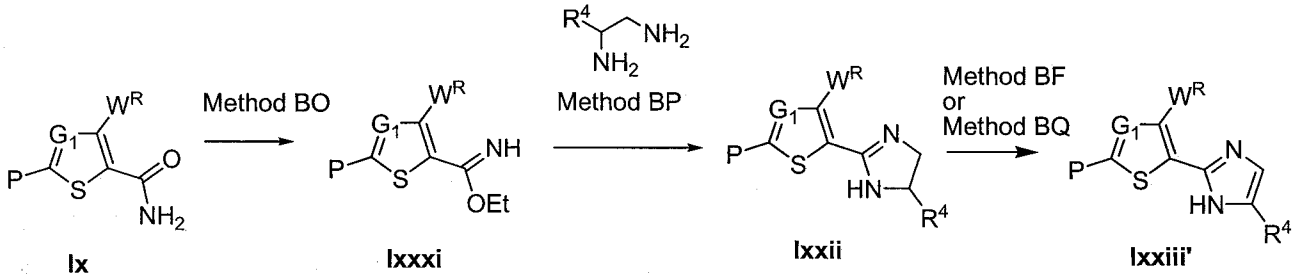


lxv lxxix lxxx lxxiii

[00306] As shown in scheme 36, treatment of thioamides **lxv**, which can be prepared by the procedure described in scheme 26 or 27, with methyl iodide affords imidothioate intermediates **lxxix** (Method BL), which may then be treated with optionally substituted aminoacetaldehyde dimethyl acetal in a suitable solvent, like acetic acid, at elevated temperature to afford intermediate amidines **lxxx** (Method BM).

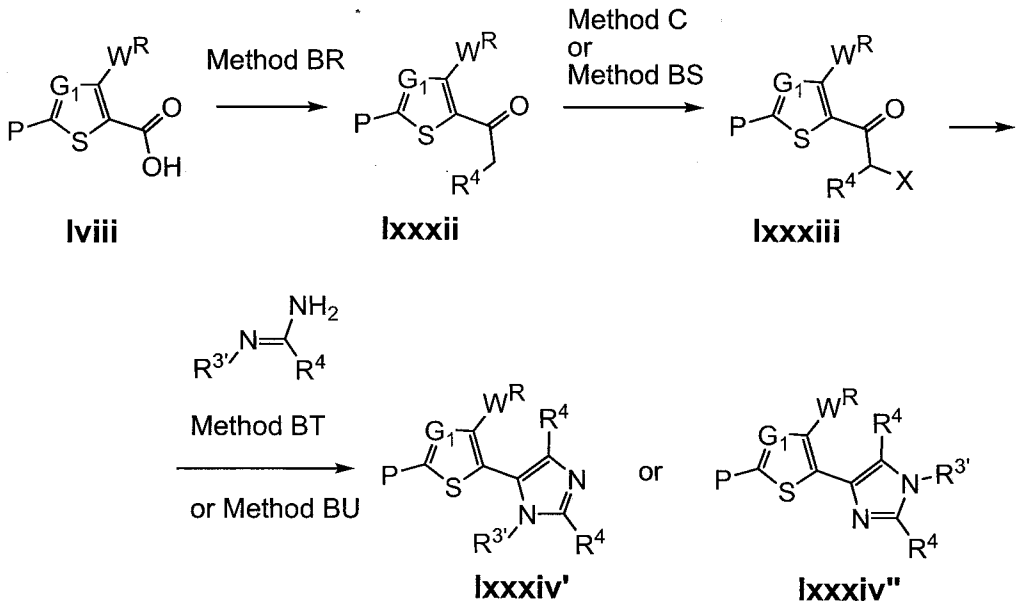
Amidines **lxxx** can then be treated with an acid, such as aqueous HCl and a suitable co-solvent, like ethanol, at elevated temperature to give imidazoles of formula **lxxiii** (Method BN).

[00307] Scheme 37: Alternative method for the construction of substituted 2-imidazolyl.



[00308] As shown in scheme 37, treatment of amides **lx**, which can be prepared by the procedure described in scheme 23, with an alkylating agent, such as Meerwein's reagent, in DCM (Method BO) gives iminoesters **lxxxi**, which can be then treated with diamines using appropriate conditions, for example ethanol at elevated temperature (Method BP) to forme dihydroimidazoles **lxxii**, which can be then oxidized in a same manner as in Method BF described in Scheme 31, or when R^4 is an appropriate leaving group, elimination can be carried out using a base, such as DBU in DCM (Method BQ).

[00309] Scheme 38: General route for the construction of substituted 4 (5)-imidazolyl.

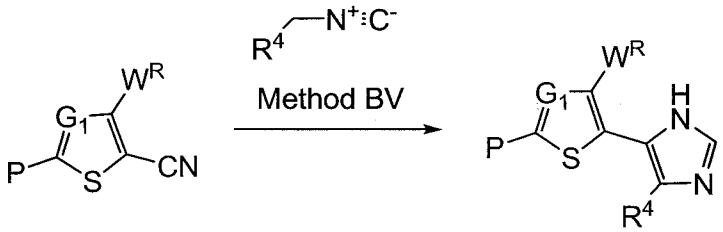


[00310] As shown in Scheme 38, acids **lviii** may be transformed to ketones **lxxxii** using a suitable synthetic sequence, for example through a coupling with *N,O*-dimethylhydroxylamine and subsequent treatment of the resulting Weinreb amides with alkyllithium or Grignard reagents in a suitable solvent, like THF (Method BR).

Ketones **lxxxii** are then halogenated with a suitable reagent, such as bromine or NBS in an appropriate solvent, like DCM (Method C) to form alpha-halogenated ketones **lxxxiii** (X = halogen). Alternatively, treatment of ketones **lxxxii** with a suitable oxidative sulfonylating agent, like hydroxy(tosyloxy)iodobenzene using suitable conditions, for example heating in acetonitrile (Method AS) affords sulfonyl esters of formula **lxxxiii** (X = OSO_2R).

Treatment of **lxxxiii** with amidine reagents in the presence of a suitable base, like potassium carbonate in a suitable solvent, such as THF-water mixture at elevated temperature or microwave irradiation affords the final imidazoles **lxxxiv'** and **lxxxiv"** (Method BT). Alternatively, compounds **lxxxiii** can be treated with large excess of amides, such as formamide using microwave irradiation to afford imidazoles **lxxxiv**'and **lxxxiv"** (Method BU).

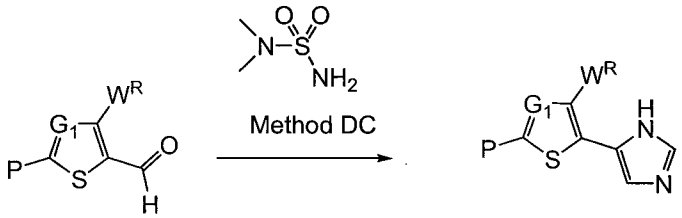
[00311] Scheme 39: Alternative method for the construction of substituted 4 (5)-imidazolyl.



lxiv **lxxxiv'"**

[00312] As shown in scheme 39, treatment of nitriles **lxiv**, which can be prepared by the procedure described in scheme 25, with isocyanates in the presence of a suitable base, such as tOBuK, in a suitable solvent, for example THF gives imidazoles of formula **lxxxiv'"**. (Method BV).

[00313] Scheme 40: Alternative method for the construction of 4-imidazolyl.

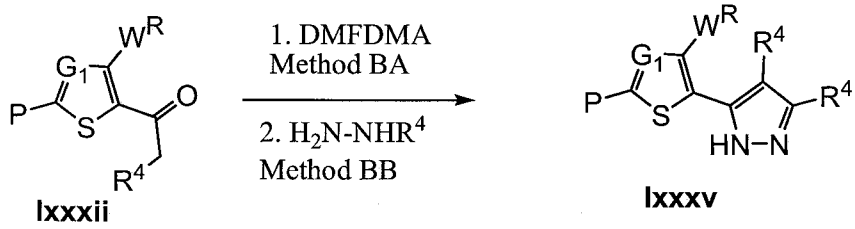


lxxvii **lxxxiv**

[00314] As shown in scheme 40, treatment of aldehydes **lxxvii** with N,N-dimethylsulfonamide at elevated temperature in a suitable solvent, for example toluene, to allow azeotropic removal of water can afford intermediate imines, that are treated with TOSMIC, a suitable base, like potassium carbonate in a suitable solvent, such as DME at elevated temperature to afford intermediate imidazole sulfonamides, that can be hydrolyzed to imidazoles **lxxxiv** with an acid, for example aqueous HBr at elevated temperature (Method DC).

[00315] Schemes 41 and 42 describe the procedures for introducing a pyrazolyl group.

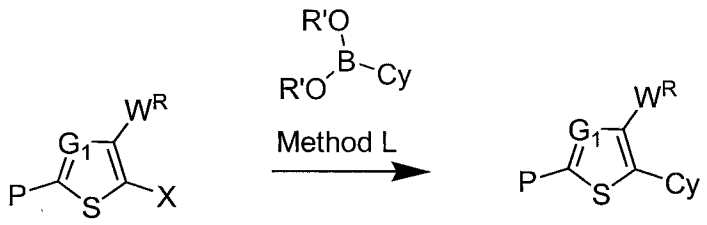
[00316] **Scheme 41: General route for the construction of 3 (5)-pyrazolyl.**



lxxxii **lxxxv**

[00317] As shown in Scheme 41, ketones **lxxxii**, which can be prepared by the procedure described in scheme 38, are treated with DMF-DMA to afford an intermediate enamines (Method BA) followed by reaction with substituted hydrazine, or hydrazine hydrate in a suitable solvent, for example acetic acid, to give pyrazoles **lxxxv** (Method BB).

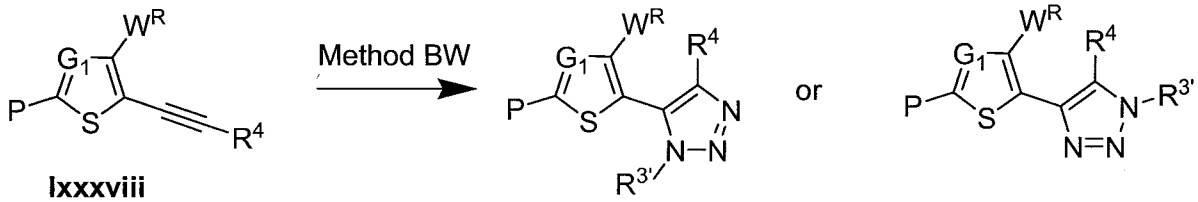
[00318] **Scvheme 42: General route for the introduction of heteroaromatic group.**



lvii **lxxxvi**

[00319] As shown in Scheme 42, halides **lvii**, which can be prepared by the procedure described in scheme 24, are treated with heteroaryl boronic acids or esters, in the presence of a suitable catalyst, for example $Pd(PPh_3)_4$, using a base, such as cesium carbonate in a suitable solvent, like dioxane-water mixture at elevated temperature to afford compounds of formula **lxxxvi** (Method L).

[00320] **Scheme 43: General route for the construction of 1,2,3-triazolyl.**

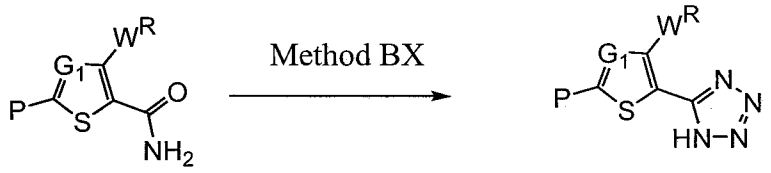


lxxxviii **lxxxix** **lxxxix'**

[00321] As shown in Scheme 43, alkynes **lxxxviii**, which can be prepared by the known Stille- or Sonogashira-coupling reaction in which a halide **lvii**, which can be prepared by the procedure described in scheme 24, and an appropriate alkyne derivative may be treated with azides, inorganic or organic a

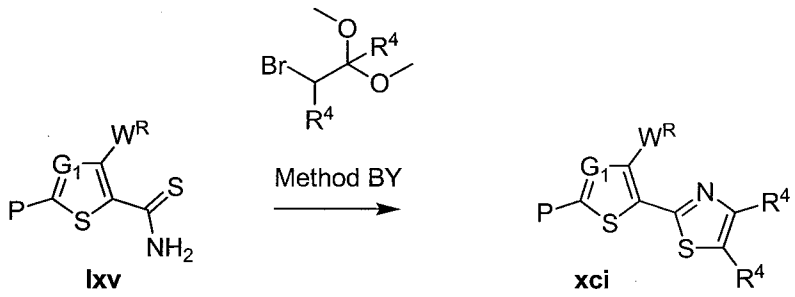
suitable solvent, such as dioxane, at elevated temperature to afford triazoles of formula **lxxxix** and **lxxxix'** (Method BW).

[00322] Scheme 44: General route for the construction of tetrazolyl.



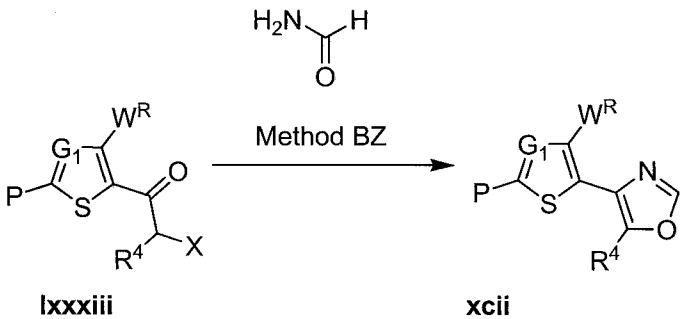
[00323] As shown in Scheme 44, amides **lx**, which can be prepared by the procedure described in scheme 23, may be treated with an azide source, for example sodium azide using a suitable Lewis acid, for example silicon tetrachloride in an appropriate solvent, such as acetonitrile to give tetrazoles **xc** (Method BX).

[00324] Scheme 45: General route for the construction of 2-thiazolyl.



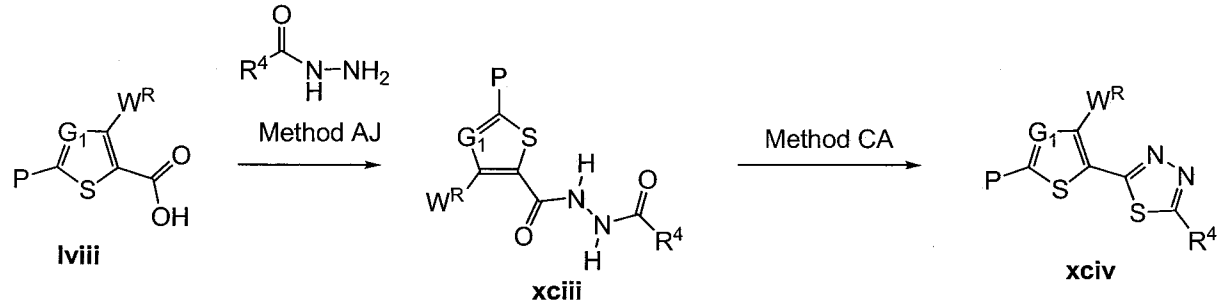
[00325] As shown in scheme 45, thioamides **lxv**, which can be prepared by the procedure described in scheme 26 or 27, are treated with substituted bromoacetaldehyde dimethyl acetals to afford thiazoles of formula **xci** (Method BY).

[00326] Scheme 46: General route for the construction of 4-oxazolyl



[00327] As shown in scheme 46, alpha-halogenated ketones **lxxxiii**, which can be prepared by the procedure described in scheme 38, may be treated with formamide under elevated temperature or microwave irradiation to afford the final 4-oxazoles **xcii** (Method BZ).

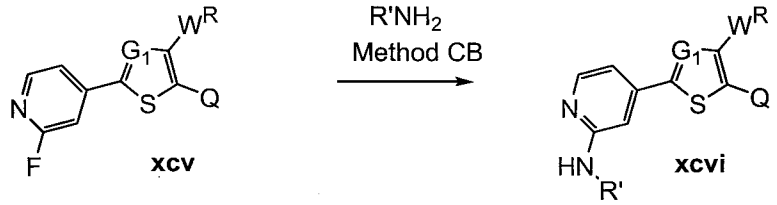
[00328] Scheme 47: General route for the construction of 1,3,4-thiadiazolyl



[00329] As shown in scheme 47, acids **lviii** are coupled with acylhydrazines using standard coupling conditions, such as EDCI, HOBt, DMF at elevated temperature to afford intermediates **xciii** (Method AJ), that are treated with Lawesson's reagent using suitable conditions, for example in toluene under reflux to afford thiadiazoles **xciv** (Method CA).

[00330] Scheme 48—51 describe general procedure for the functional group transformation on HY.

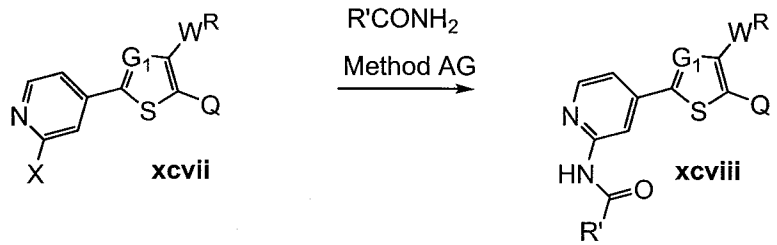
[00331] Scheme 48: General method for the introduction of amino group to 2-fluoropyridyl



[00332] Scheme 48 shows a general route for the transformation of 2-fluoropyridyl to 2-substituted aminopyridyl to give the compounds of formula **xcvi**.

As shown in Scheme 48, compounds **xcv** can be treated with amines at elevated temperature or under microwave irradiation to give 2-aminopyridines **xcvi** (Method CB).

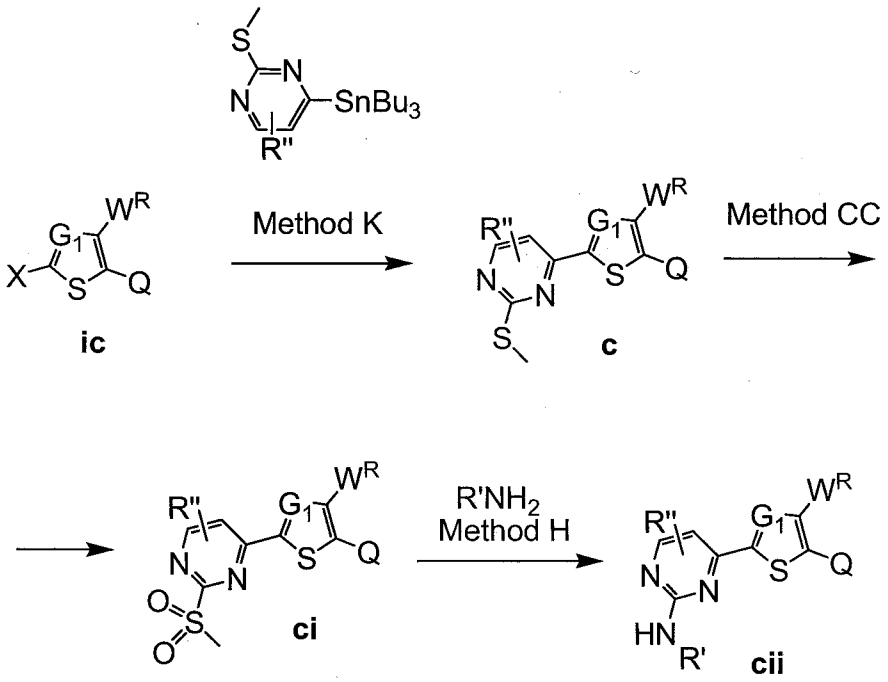
[00333] Scheme 49: General method for the introduction of 2-acylaminopyridines by Buchwald reaction



[00334] Scheme 49 shows a general route for the transformation of 2-halopyridyl to 2-acylaminopyridyl by Buchwald reaction to give the compounds formula **xcviii**.

As shown in Scheme 49, compounds **xcvii** can be treated with amides or carboxamides in the presence of a suitable catalyst, such as Pd_2dba_3, XantPhos, base like cesium carbonate in an appropriate solvent, for example dioxane at elevated temperature or under microwave irradiation to give acylaminopyridines **xcviii** (Method AG).

[00335] Scheme 50: General method for the synthesis of 2-aminopyrimidyl thiophene / thiazole

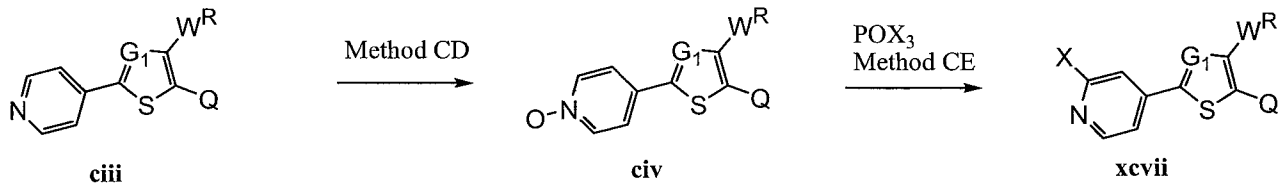


[00336] As shown in Scheme 50, compounds **ic** can be coupled with stannanes under suitable conditions, for example $Pd(PPh_3)_4$, CuI, LiCl in dioxane at elevated temperature to give compounds **c** (Method K).

Oxidation of thioethers **c** to sulfones **ci** can be achieved using a suitable oxidant, for example mCPBA in DCM (Method CC).

Methanesulfonyl group of sulfones **ci** can be displaced by treatment with amines in a suitable solvent, for example THF to afford 2-aminopyrimidines **cii** (method H).

[00337] Scheme 51: General method for the introduction of 2-halo substituent on 4-pyridyl group

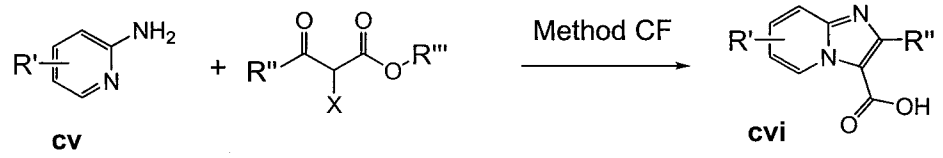


[00338] Scheme 51 shows a general route for the transformation of 4-pyridyl to 2-halo-4-pyridyl compounds formula **xcvii**.

As shown in Scheme 51, compounds **ciii** can be treated with an oxidant, for example mCPBA in a suitable solvent, such as DCM to afford intermediate N-oxides **civ** (Method CD), which may be halogenated in 2-position using phosphoryl halides, for example phosphoryl chloride, under elevated temperature to afford compounds of formula **xcvii** (Method CE).

[00339] Schemes 52—58 describe the procedures for the synthesis of building blocks for HY.

[00340] **Scheme 52: General method for the synthesis of imidazo[1,2-a]pyridine building blocks.**

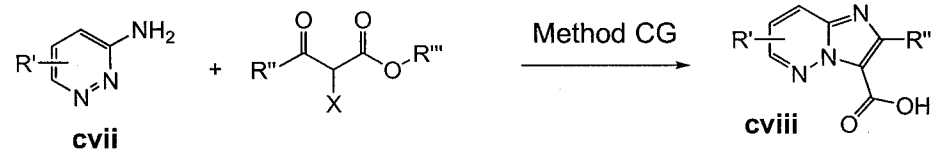


cv **cvi**

[00341] Scheme 52 shows a general method for the synthesis of imidazo[1,2-a]pyridines **cvi**.

As shown in Scheme 52, 2-aminopyridines **cv** may be condensed with alpha-halogenated beta-ketoesters in a suitable solvent, for example ethanol, at elevated temperature to afford intermediate esters, that are hydrolyzed using standard conditions, such as aqueous sodium hydroxide in THF followed by acidic workup to give acids **cvi** (Method CF).

[00342] **Scheme 53: General method for the synthesis of imidazo[1,2-b]pyridazine building blocks**

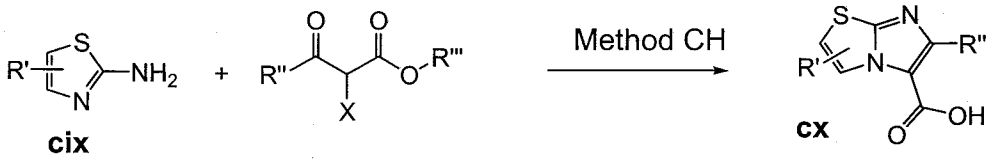


cvii **cviii**

[00343] Scheme 53 shows a general method for the synthesis of imidazo[1,2-b]pyridazines **cviii**.

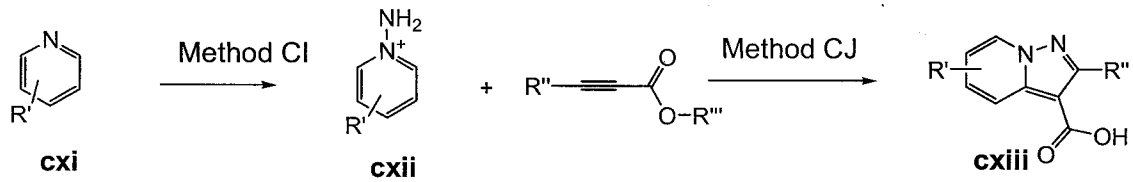
As shown in Scheme 53, 2-aminopyridazines **cvii** may be condensed with α-halogenated beta-ketoesters in a suitable solvent, for example ethanol at elevated temperature to afford intermediate esters, that are hydrolyzed using standard conditions, such as aqueous sodium hydroxide in THF followed by acidic workup to give acids **cviii** (Method CG).

[00344] **Scheme 54: General method for the synthesis of imidazo[2,1-b][1,3]thiazole building blocks**



[00345] Scheme 54 shows a general method for the synthesis of imidazo[2,1-b][1,3]thiazoles **cx**. As shown in Scheme 54, 2-aminothiazoles **cix** may be condensed with α-halogenated β-ketoesters in a suitable solvent, for example ethanol, at elevated temperature to afford intermediate esters, which may be hydrolyzed using standard conditions, such as aqueous sodium hydroxide in THF followed by acidic workup to give acids **cx** (Method CH).

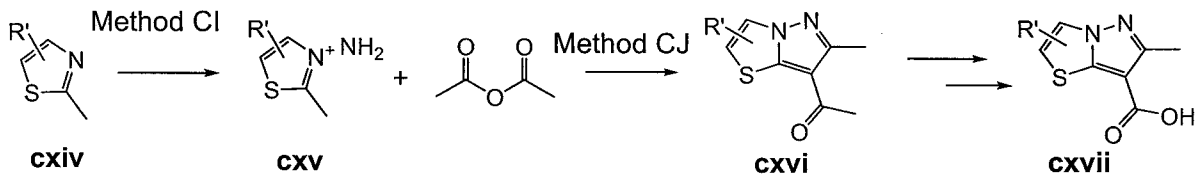
[00346] **Scheme 55: General method for the synthesis of pyrazolo[1,5-a]pyridine building blocks**



[00347] Scheme 55 shows a general method for the synthesis of pyrazolo[1,5-a]pyridines **cxiii**. As shown in Scheme 55, pyridines **cxi** may be *N*-aminated with a suitable agent, such as *O*-(mesitylsulfonyl)hydroxylamine using appropriate conditions, for example toluene or ethyl acetate as solvent (Method CI).

Resulting *N*-aminopyridinium salts **cxii** may then be condensed with alkynylcarboxylic acid esters with a suitable base, such as potassium carbonate in a suitable solvent, for example DMF to afford intermediate esters, which may be hydrolyzed using standard conditions, such as aqueous sodium hydroxide in THF followed by acidic workup to give acids **cxiii** (Method CJ).

[00348] **Scheme 56: General method for the synthesis of pyrazolo[5,1-b][1,3]thiazole building blocks**

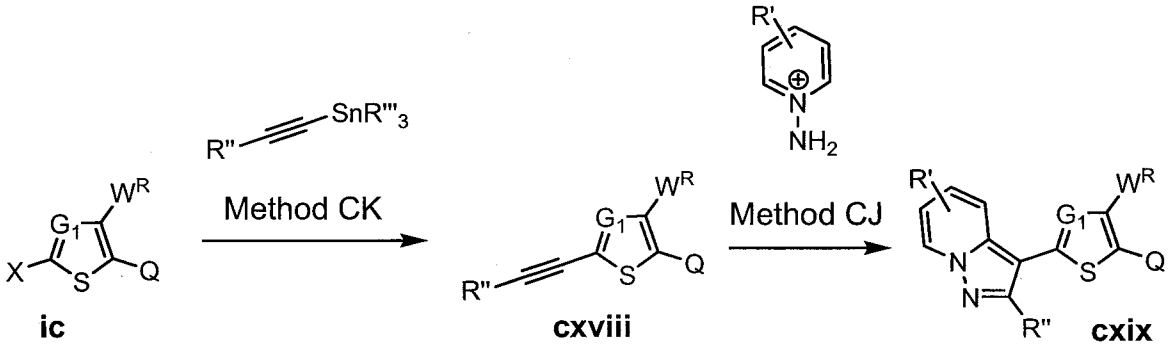


[00349] Scheme 56 shows a general method for the synthesis of pyrazolo[5,1-b][1,3]thiazoles **cxvii**. As shown in Scheme 56, 2-methylthiazoles **cxiv** may be *N*-aminated with a suitable agent, such as *O*-(mesitylsulfonyl)hydroxylamine using appropriate conditions, for example toluene or ethyl acetate as solvent (Method CI).

Resulting *N*-aminothiazolium salts **cxv** can then be condensed with acetic anhydride and potassium

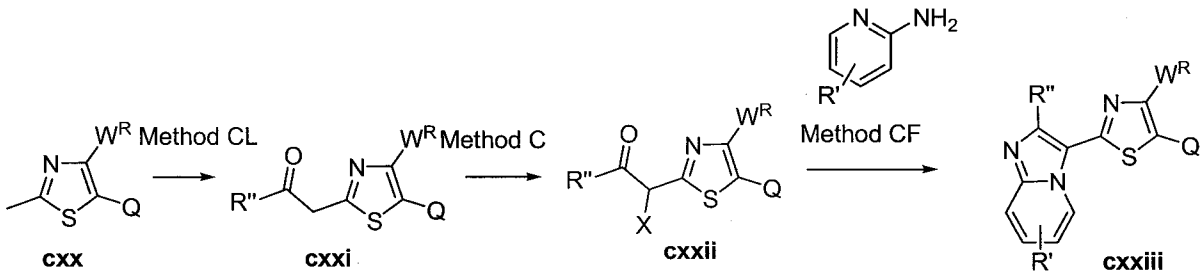
acetate at elevated temperature to afford methyl ketone intermediate **cxvi** (Method CJ), which can be converted to carboxylic acid **cxvii** moiety by well known functional transformation of methyl ketone to carboxylic acid.

[00350] Scheme 57: Alternative method for the synthesis of pyrazolo[5,1-b][1,3]thiazole derivatives



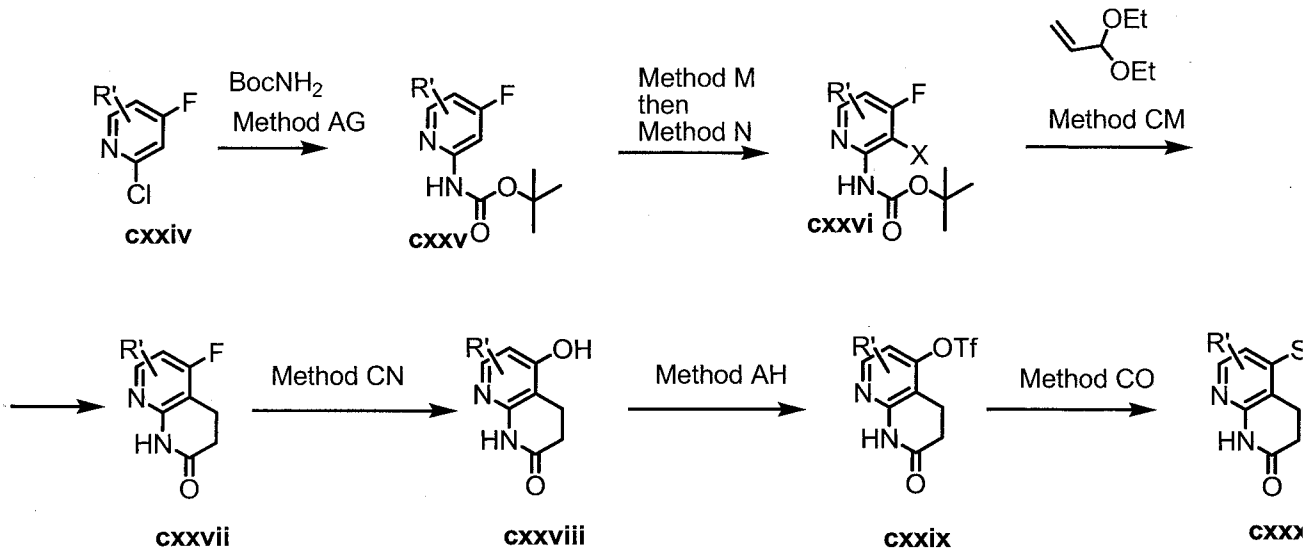
[00351] Scheme 57 shows an alternative method for the synthesis of pyrazolopyridines **cxix**. As shown in Scheme 57, halides **ic** are treated with alkynyl stannanes in the presence of a suitable catalysts, such as $Pd(PPh_3)_4$, CuI, with LiCl in an appropriate solvent, like dioxane at elevated temperature to give alkynes of formula **cxviii** (Method CK). Alkynes **cxviii** are then coupled with *N*-aminopyridinium salts with a base, like potassium carbonate in a suitable solvent, for example DMF to afford compounds of formula **cxix** (Method CJ).

[00352] Scheme 58:Alternative method for the synthesis of imidazo[1,2-a]pyridine building blocks.



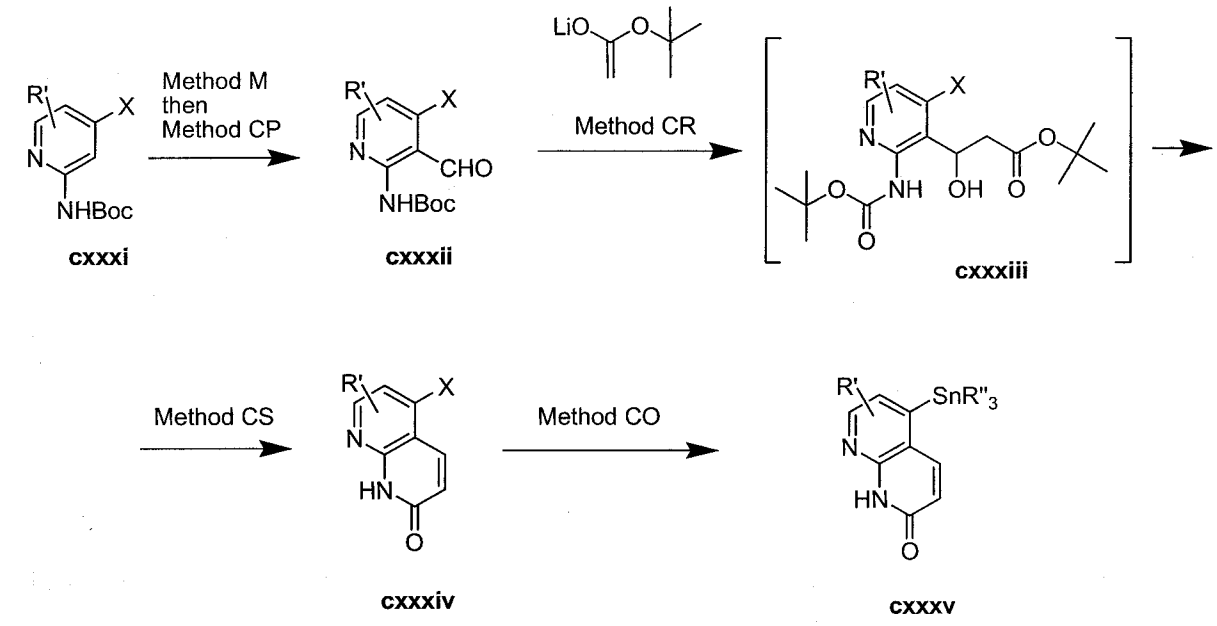
[00353] Scheme 58 shows an alternative method for the synthesis of imidazolopyridines **cxxiii**. As shown in Scheme 58, 2-methylthiazoles **cxx** may be deprotonated with a suitable reagent, such as *n*-BuLi and subsequently treated with Weinreb amides in a suitable solvent, such as THF to give ketones **cxxi** (Method CL). Halogenation of ketones can be achieved using standard conditions, for example NBS in DCM (Method C) and the resulting haloketones **cxxii** are then treated with aminopyridines in a suitable solvent, for example ethanol at elevated temperature to give compounds of formula **cxxiii** (Method CF).

[00354] Scheme 59: General method for the synthesis of bicyclic lactam building blocks



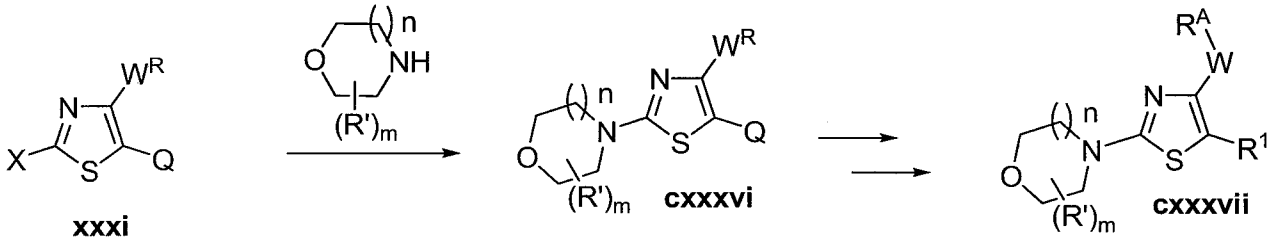
[00355] Scheme 59 shows a general method for the synthesis of bicyclic lactam building blocks **cxxix** and **cxxx**. As shown in Scheme 59, substituted 2-chloro-4-fluoropyridines can be amidated, for example with $BocNH_2$, Pd_2dba_3 and a suitable ligand, such as X-Phos in the presence of a base, for example cesium carbonate in an appropriate solvent, like dioxane to afford Boc-protected 2-aminopyridines **cxxv** (Method AG). Compounds **cxxv** can be deprotonated, for example using *n*-BuLi/TMEDA in THF at low temperature (Method M) and then quenched with a molecule of halogen, such as iodine in THF (Method N) to give halogenated compounds **cxxvi**. Compounds **cxxvi** can be coupled with diethoxypropene using a suitable Pd catalyst, such as Di-mu-chlorobis[5-hydroxy-2-[1-(hydroxyimino-kappaN)ethyl]phenyl-kappaC]palladium(II) dimer with an appropriate base, like *N,N*-diisopropylethylamine in a suitable solvent, for example DMF-water mixture (Method CM) to afford lactams of formula **cxxvii**. Transformation of fluoro **cxxvii** into hydroxyl analogs **cxxviii** can be carried out using a standard procedure, for example treatment with benzyl alcohol in the presence of a base, such as sodium hydride at elevated temperature and subsequent debenzylation, such as using hydrogenation with Pd/C catalyst in a suitable solvent, such as ethanol (Method CN). Triflates **cxxix** can be formed by treatment of **cxxviii** with a suitable reagent, for example triflic anhydride using appropriate conditions, such as pyridine as a base in DCM (Method AH). Triflates **cxxix** can be coupled with stannanes **xxix**, obtained in Scheme 6 using standard Stille conditions (Method K). Alternatively, triflates **cxxix** can be transformed into stannanes **cxxx** using a suitable method, such as heating with hexamethyldistannane, $Pd(PPh_3)_4$ in a suitable solvent, like THF (Method CO). Stannanes **cxxx** can be then coupled with thiophene/thiazole halides **ic**, which can be prepared by the procedures described in schemes 3, 5, 6 using standard Stille conditions (Method K).

[00356] Scheme 60: Alternative method for the synthesis of bicyclic lactam building blocks



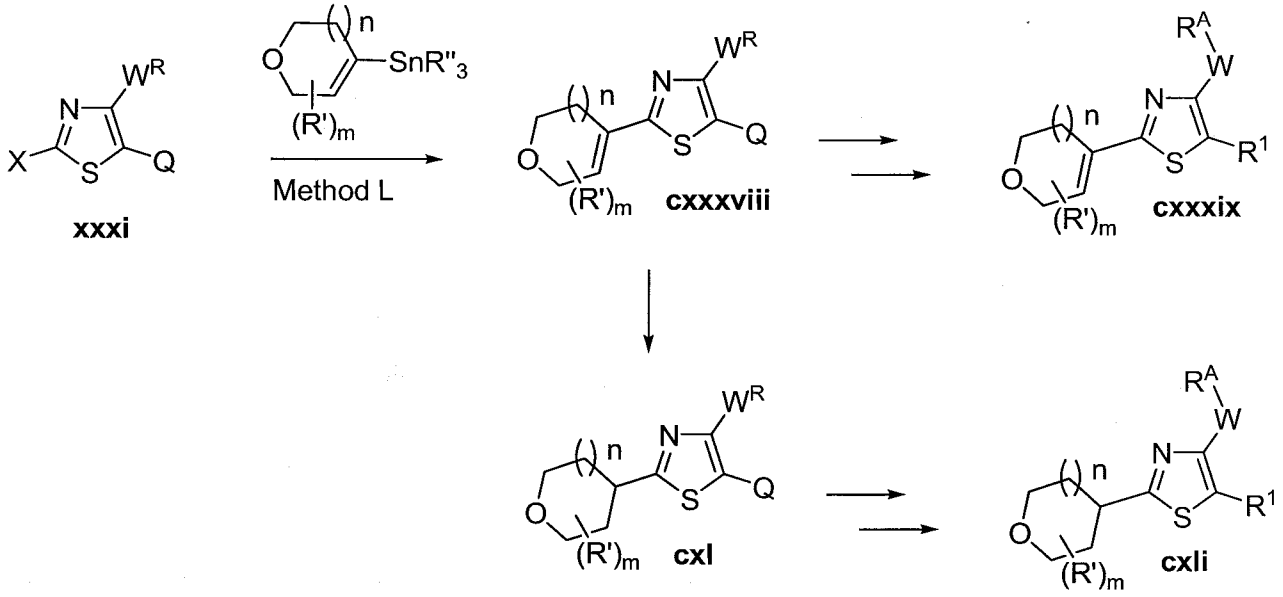
[00357] Scheme 60 shows an alternative method for the synthesis of bicyclic lactam building blocks **cxxxv**. As shown in Scheme 60, compounds **cxxxi** can be deprotonated with a suitable reagent, such as *n*-BuLi in THF at low temperature (Method M) and then treated with DMF to produce carbaldehydes **cxxxii** (Method CP). Aldehyde group in **cxxxii** can be then treated with enolate generated from *t*-Butylacetate and LDA in a suitable solvent, such as THF at low temperature (Method CR) to form intermediate β-hydroxyesters **cxxxiii** that can be cyclized to lactams **cxxxiv** using an acid, such as HCl, in water at elevated temperature (Method CS). Halides **cxxxiv** can be coupled with stannanes **xxix**, obtained in Scheme 6 using standard Stille conditions (Method K). Alternatively, transformation of aryl halides **cxxxiv** to stannanes **cxxxv** can be carried out using hexamethyldistannane, $Pd(PPh_3)_4$ in a suitable solvent, like THF (Method CO). Stannanes **cxxxv** can be then coupled with thiophene/thiazole halides **ic**, which can be prepared by the procedures described in schemes 3, 5, 6 using standard Stille conditions (Method K).

[00358] **Scheme 61: General method for the preparation of 2-aminothiazoles**



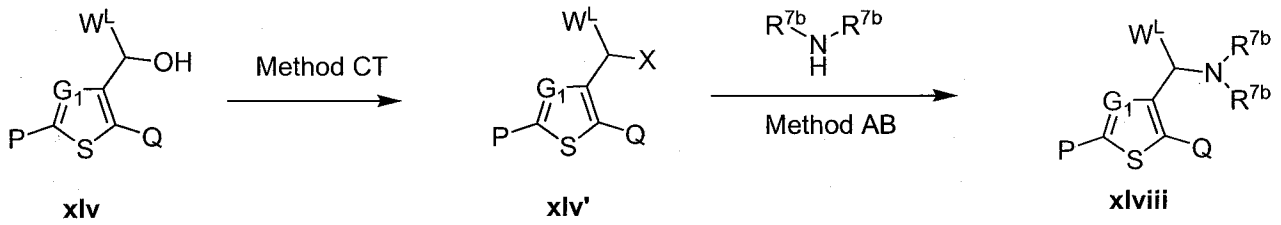
[00359] Scheme 61 shows a general method for preparation of compounds of formula **cxxxvii**. As shown in scheme 61, 2-halothiazoles are treated with amines at elevated temperature, either neat, or in a suitable solvent, such as NMP with an appropriate base, for example K_2CO_3 (Method H) to afford 2-aminothiazoles **cxxxvi**, that can be further transformed to compounds **cxxxvii** using generally known methods.

[00360] **Scheme 62: General method for coupling of halothiazoles with vinylstannanes**



[00361] Scheme 62 shows a general method for preparation of compounds of formula **cxxxix** and **cxli**. As shown in Scheme 62, compounds **xxxi** can be coupled with vinylstananes under suitable conditions, for example $Pd(PPh_3)_4$, CuI, LiCl in dioxane under elevated temperature to give alkenes cxxxviii (Method K), that can be further transformed to compounds **cxxxix** by generally known methods. Alternatively, hydrogenation of **cxxxviii**, for example using Pd/C as catalyst in a suitable solvent, such as ethanol (Method V) can afford compounds **cxl**, that can be further transformed to **cxli** by generally known methods.

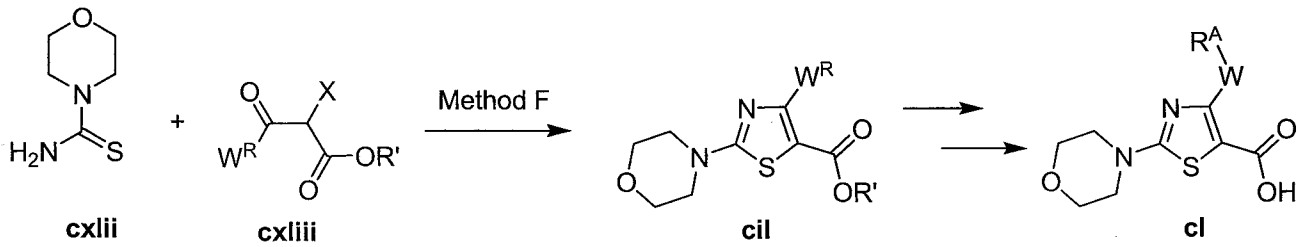
[00362] **Scheme 71: General method for the synthesis of amines**



xlv xlv' xlviii

[00363] Scheme 71 shows a general method for the synthesis of amines **xlviii**. As shown is Scheme 71, alcohols **xlv** can be transformed to halides **xlv'** using treatment with a suitable reagent, such as PCl_5 in a suitable solvent, such as DCM. Halides **xlv'** are then treated with amines at elevated temperature to provide target amines **xlviii** (Method AB).

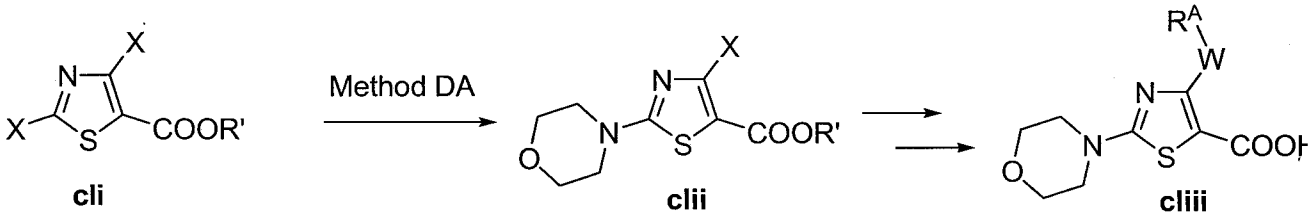
[00364] **Scheme 63: General method for the synthesis of substituted thiazoles**



cxlii cxliii cil cl

[00365] Scheme 63 shows a general route for the synthesis of compounds of formula **cl**. Thioamide **cxlii** can be treated with alpha-halogenated carbonyl compounds **cxliii** in a suitable solvent, such as isopropanol at elevated temprerature to give thiazoles **cil**. (Method F). A conversion reaction from **cil** to compounds **cl** can be performed by a combination of generally known functional group conversion reactions.

[00366] **Scheme 64: General method for introduction of morpholine to 2-position of thiazole core.**

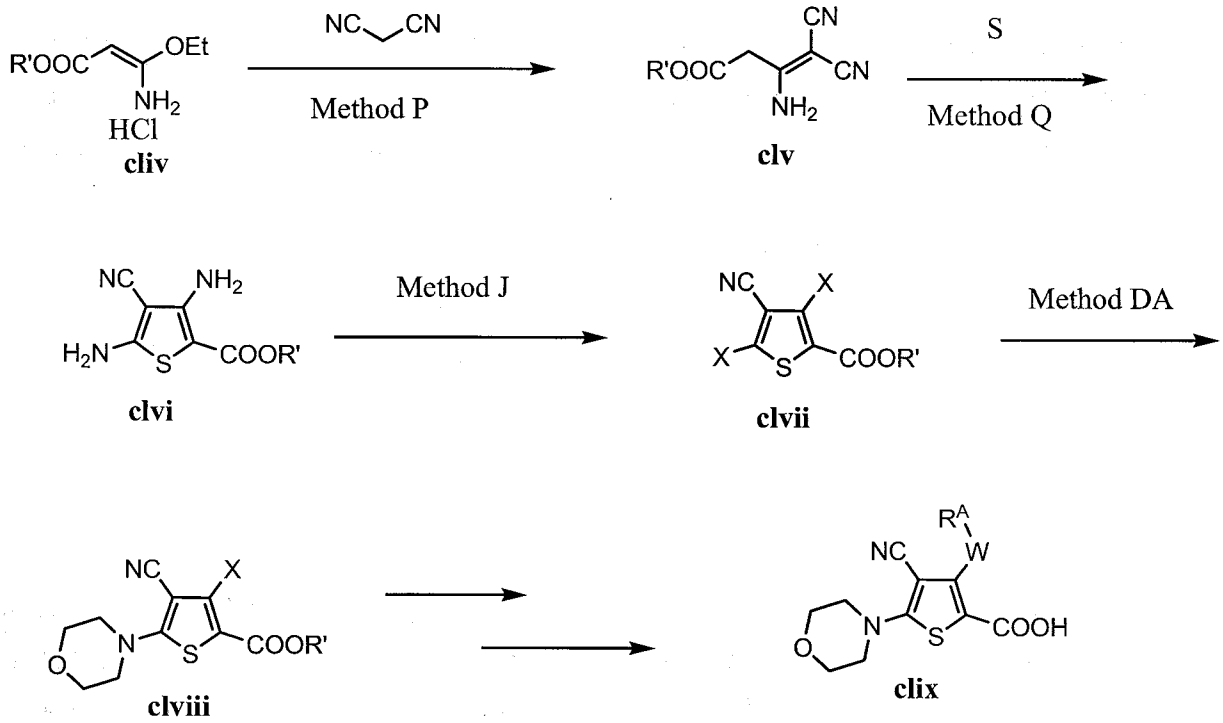


cli clii cliii

[00367] Scheme 64 shows a general route for introducing morpholine to the 2-position of thiazole core scaffold. Dihalothiazole esters, such as Methyl 2,4-dibromo-5-thiazolecarboxylate can be treated with morpholine at elevated temperature, with a suitable base, such as cesium carbonate in THF or other

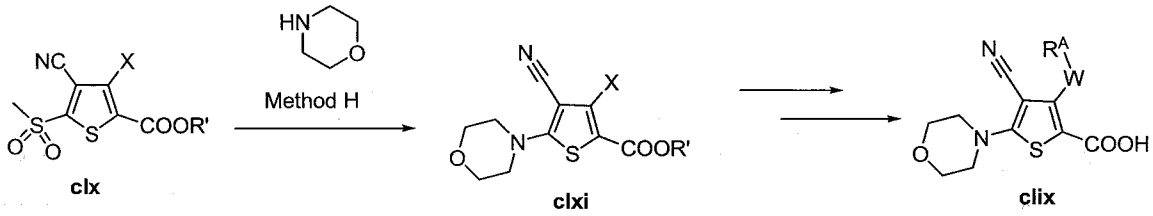
appropriate solvent (Method DA) to afford compounds of formula **clii**. Compounds **clii** can be then transformed into compounds **cliii** using generally known functional group conversion reactions.

[00368] Scheme 65: General method for the synthesis of 3-cyanothiophenes



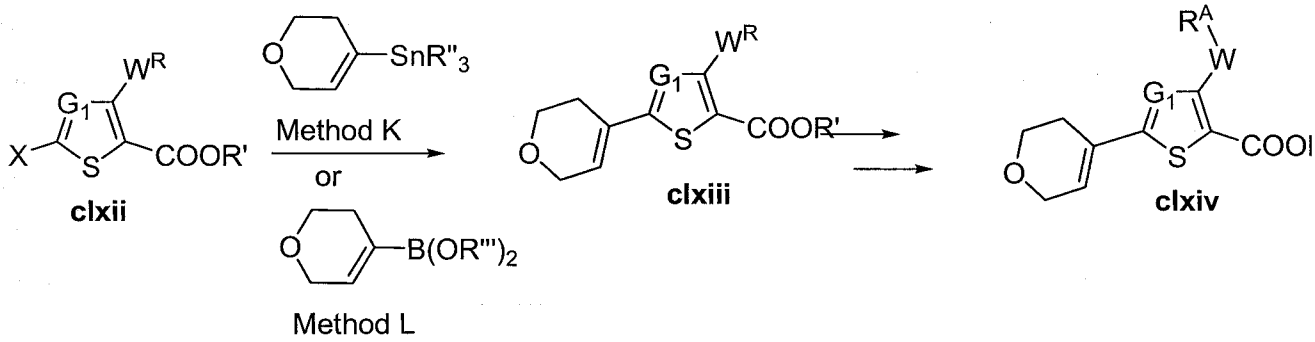
[00369] Scheme 65 describes the procedure for the synthesis of 3-cyanothiophenes **clix**. Substituted alkoxyethenamine **cliv** can be treated with malononitrile in the presence of a suitable base, such as TEA, in a suitable solvent, like chloroform, at elevated temperature to afford substituted aminoethylene malononitriles **clv** (Method P), that are treated with sulfur under suitable conditions, such as DMF and elevated temperature, to give diaminocyanothiophenes **xclvi** (Method Q). Diamines **clvi** may then be subjected to a Sandmeyer reaction using appropriate reagents, such as copper(II)bromide, amyl nitrite in ACN at elevated temperature (Method J) to afford compounds of formula **clvii**. Dihalocyanothiophenes can be then treated with morpholine at elevated temperature, with a suitable base, such as cesium carbonate in THF or other appropriate solvent (Method DA) to afford compounds of formula **clviii**. Compounds **clviii** can be then transformed into compounds **clvix** using generally known functional group conversion reactions.

[00370] Scheme 66: Alternative method for the synthesis of cyanothiophenes



[00371] Scheme 66 describes a procedure for the introduction of morpholine to 3-cyanothiophene analogs. As shown in Scheme 66, sulfones of formula **clx** (synthetic examples given in Mansanet et al, WO 2005070916) can be treated with morpholine in a suitable solvent, *e.g.*, THF, at elevated temperature (Method H) to give **clxi**. Conversion reactions from **clxi** to compounds **clix** can be performed, for example, by a combination of generally known functional group conversion reactions.

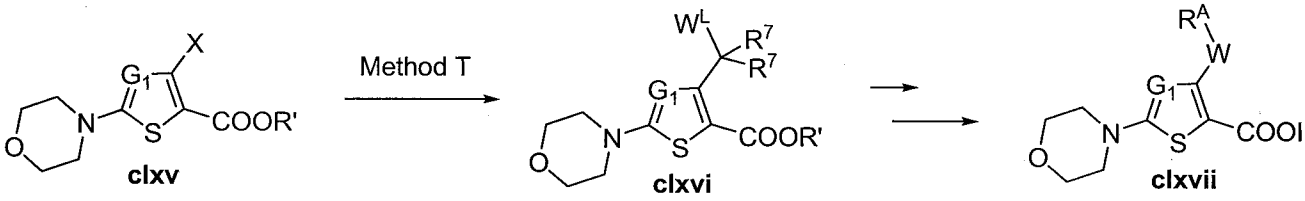
[00372] Scheme 67: General method for coupling of halothiophenes/ thiazoles with vinylstannanes / boronic esters



[00373] Scheme 67 shows a general method for preparation of compounds of formula **clxiv**. As shown in Scheme 67, compounds **clxii** can be coupled with vinylstananes under suitable conditions, for example $Pd(PPh_3)_4$, CuI, LiCl in dioxane under elevated temperature to give alkenes **clxiii** (Method K). Alternatively, Suzuki conditions, such as $Pd(PPh_3)_4$, $CsCO_3$, dioxane at elevated temperature (Method L)

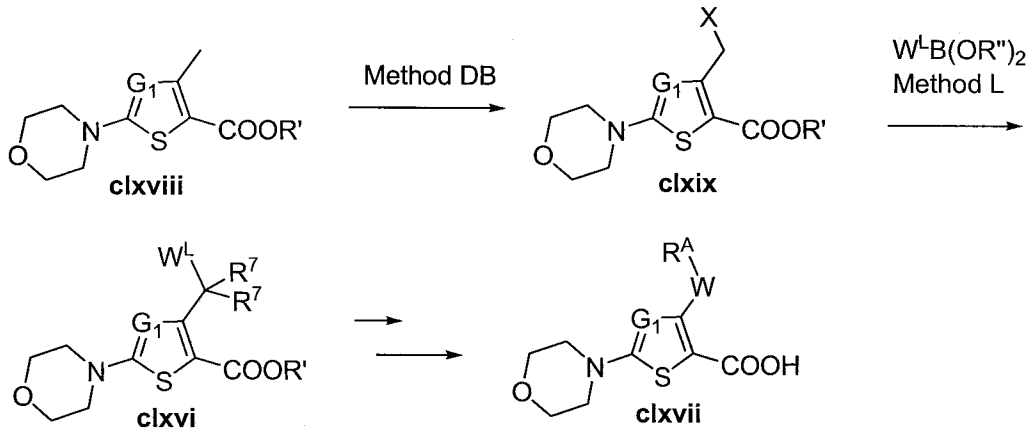
can be used. Compounds **clxiii** can be then further transformed to compounds **clxiv** by generally known methods.

[00374] Scheme 68: General method for introducing carbon functionality to halogenated thiophenes / thiazoles.



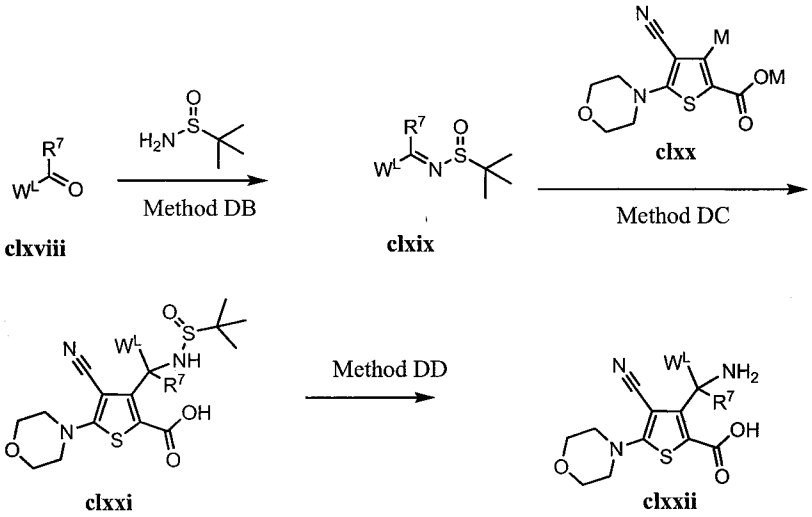
[00375] As shown in Scheme 68 carbon functionality can be introduced by the well known Negishi cross-coupling technique. Halogenated thiophenes / thiazoles **clxv** can be treated with alkyl zinc halides using Pd catalyst, such as $Pd(tBu_3P)_2$ under standard Negishi coupling conditions, such as THF at elevated temperature (Method T) to afford compounds **clxvi**, that can be further transformed to compounds **clxvii** using generally known methods.

[00376] Scheme 69: Alternative method for introducing carbon functionality to thiophenes / thiazoles.



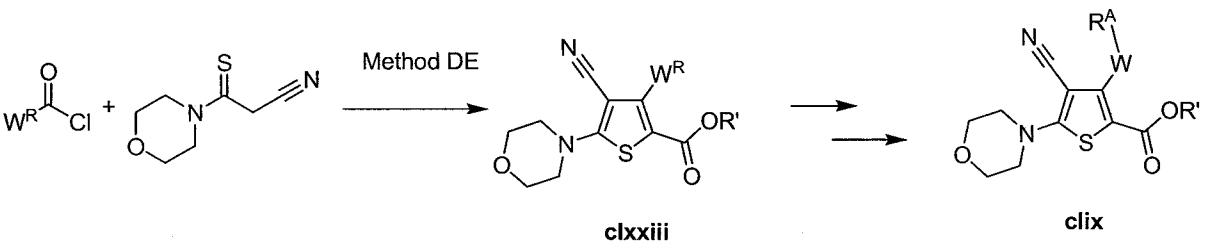
[00377] As shown in Scheme 69, methyl substituent of thiophenes/thiazoles **clxviii** can be halogenated using a suitable reagent, for example NBS with a radical source, such as AIBN in an appropriate solvent, like DCM (Method DB) to afford halides **clxix**. Halides **clxix** can be then coupled with boronic acids or esters using the well known Suzuki cross-coupling technique, for example $Pd(PPh_3)_4$, Cs_2CO_3, dioxane-water at elevated temperature (Method L) to afford compounds **clxvi**, that can be further transformed to compounds **clxvii** using generally known methods.

[00378] Scheme 70: General method for the synthesis of amino acids



[00379] As shown in Scheme 70, aldehydes or ketones **clxx** can be treated with 2-Methyl-2-propanesulfinamide in the presence of a suitable Lewis acid, such as $Ti(OiPr)_4$ in anhydrous THF, or other suitable solvent to afford sulfinamides **clxixi** (Method DC), that can be subsequently treated with thiophene metal compounds **clxxii** (Method DD), obtained from corresponding thiophene halides through halogen-metal exchange, for example from thiophene bromide using an excess of phenyllithium at low temperature. Formed sulfinyl amines **clxxiii** can be then treated with an acid, such as HCl in dioxane with an optional co-solvent, for example DCM (Method DE) to afford amino acids **clxxiv**.

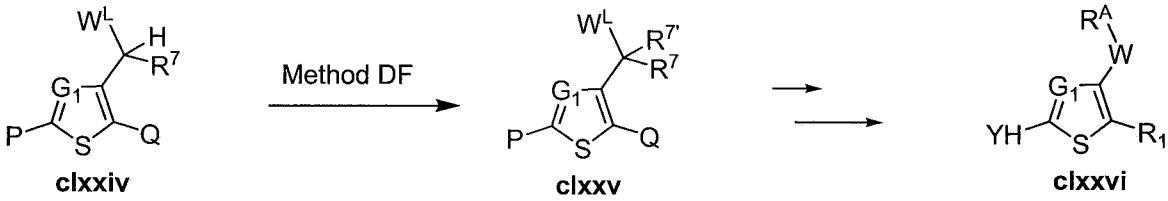
[00380] Scheme 72: Alternative method for the synthesis of cyanothiophenes



[00381] As shown in Scheme 72, acyl halides can be coupled with thiomorpholine and alkylhaloacetate in the presence of a suitable base, such as diisopropylamine in an appropriate solvent, for example MeCN at elevated temperature to afford cyanothiophenes **clxxiii** (Method DE). A conversion

reaction from **clxxiii** to compounds **clix** can be performed by a combination of generally known functional group manipulations.

[00382] Scheme 73: General method for benzylic alkylation

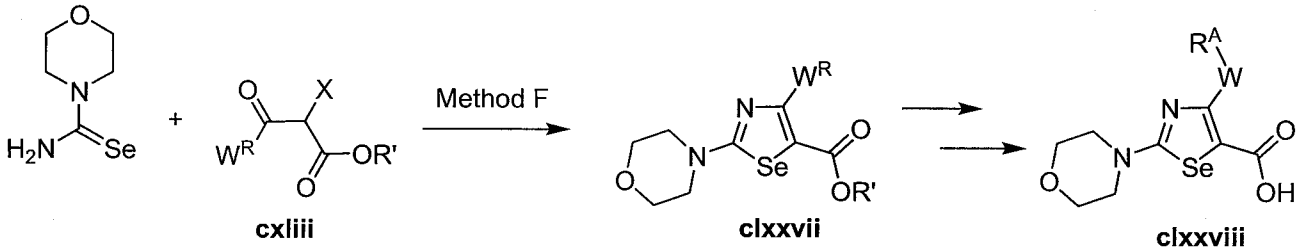


clxxiv **clxxv** **clxxvi**

[00383] As shown in Scheme 73, compounds **clxxiv** (where W^L is an aromatic or heteroaromatic group) can be deprotonated using a suitable base, such as KO*t*Bu in an appropriate solvent, for example THF and subsequently alkylated using an alkyl halide $R^{7'}$-X (Method DF) to afford products of benzylic alkylations **clxxv**. Compounds **clxxv** can be further transformed to compounds **clxxvi** using generally known methods.

[00384]

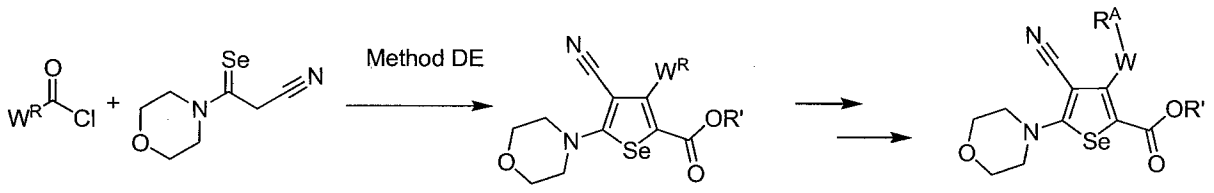
[00385] Scheme 74: General method for the synthesis of substituted selenazoles



cxliii **clxxvii** **clxxviii**

[00386] Scheme 74 shows a general route for the synthesis of compounds of formula **clxxvii**. Selenoamide can be treated with alpha-halogenated carbonyl compounds **cxliii** in a suitable solvent, such as isopropanol at elevated temprerature to give selenazoles **clxxvii**. (Method F). A conversion reaction from **clxxvii** to compounds **clxxviii** can be performed by a combination of generally known functional group manipulations.

[00387] Scheme 75: General method for the synthesis of selenophenes



clxxix **clxxx**

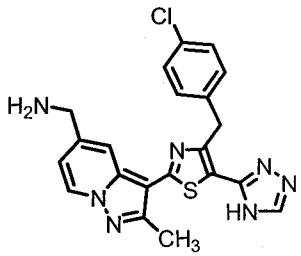
[00388] As shown in Scheme 75, acyl halides can be coupled with selenomorpholine building block and alkylhaloacetate in the presence of a suitable base, such as diisopropylamine in an appropriate

solvent, for example MeCN at elevated temperature to afford selenophenes **clxxix** (Method DE). A conversion reaction from **clxxix** to compounds **clxxx** can be performed by a combination of generally known functional group manipulations.

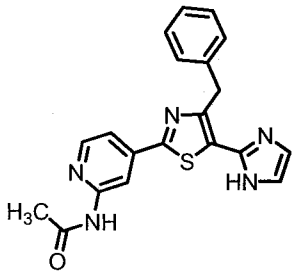
[00389] EXAMPLES

[00390] Table 1 below depicts certain compounds represented by compounds of general formula **IA** and **IB**.

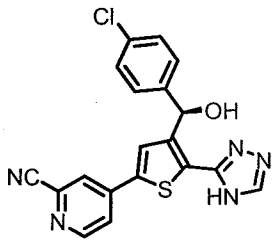
[00391] Table 1



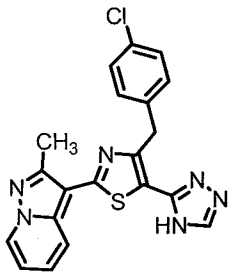
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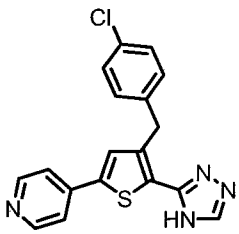
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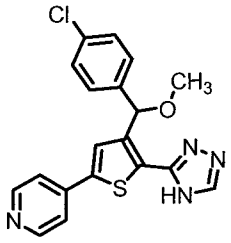
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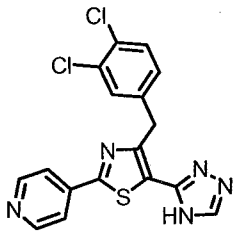
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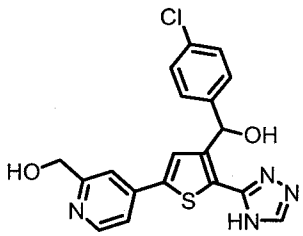
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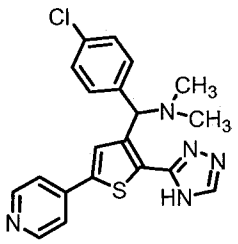
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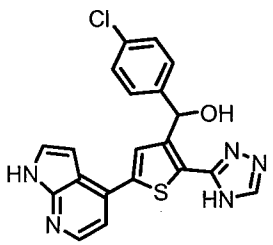
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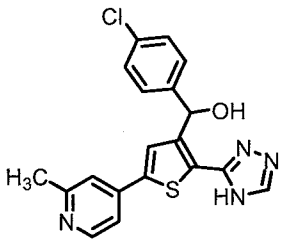
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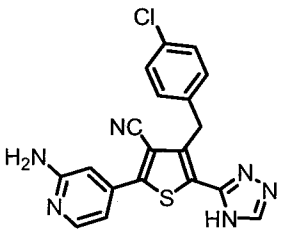
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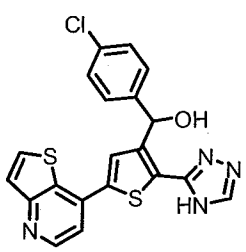
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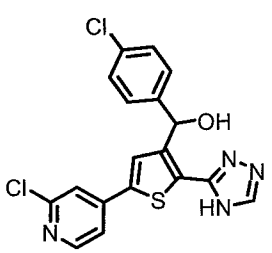
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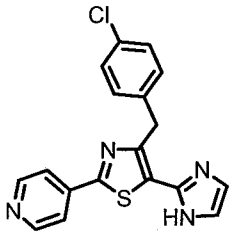
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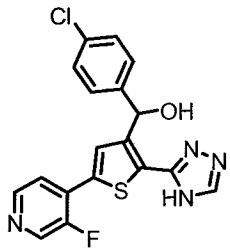
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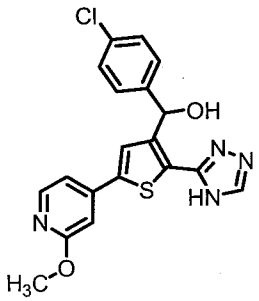
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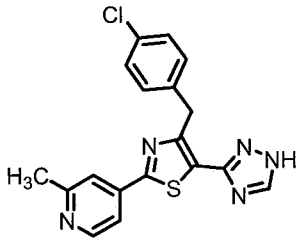
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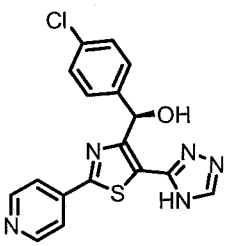
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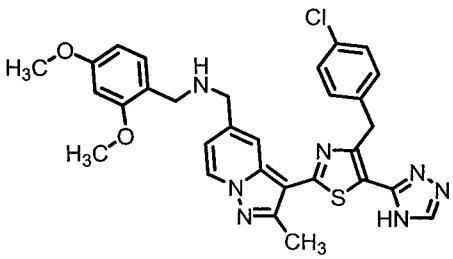
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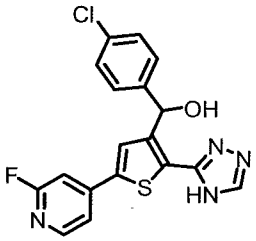
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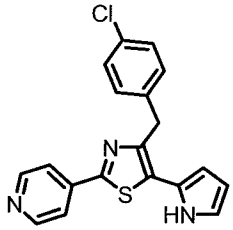


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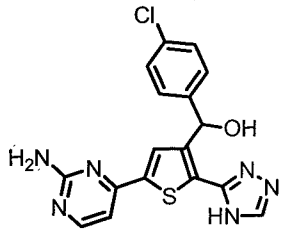


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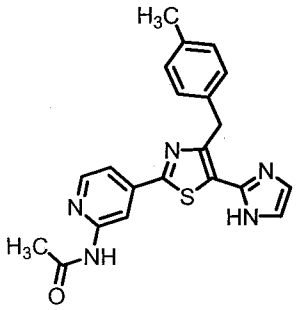




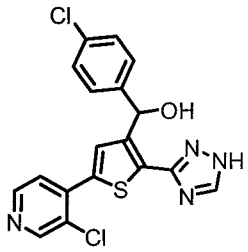
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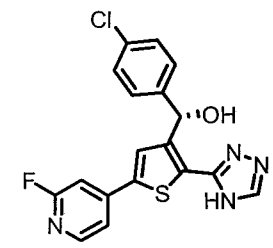
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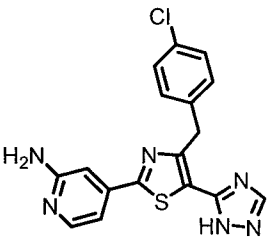
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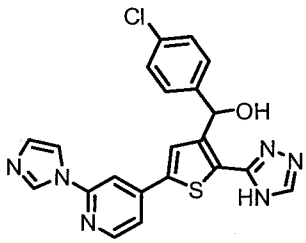
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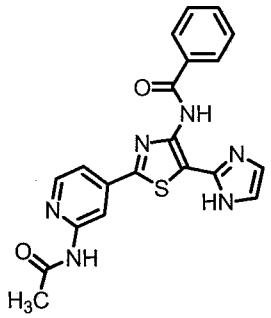


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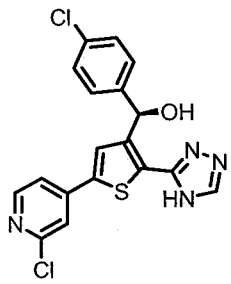
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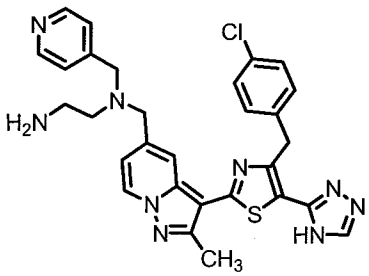




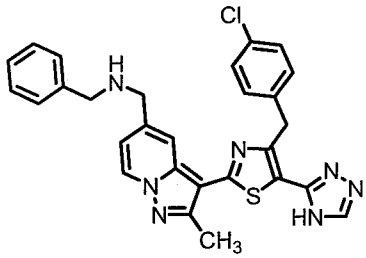
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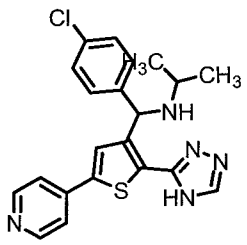
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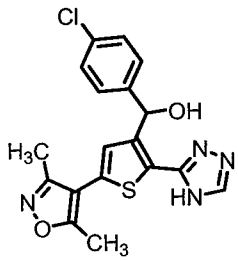
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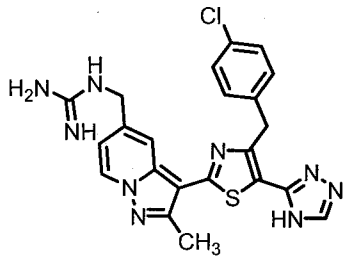
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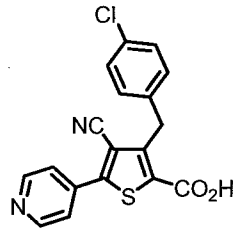
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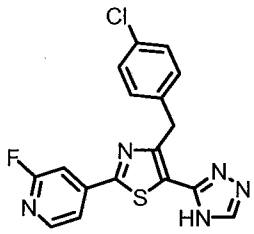
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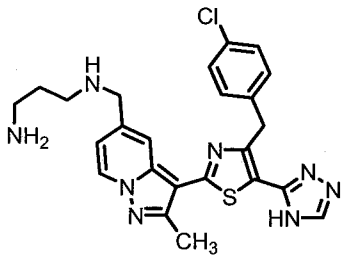
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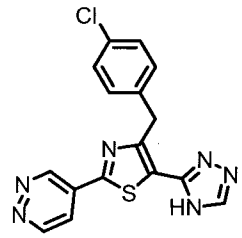
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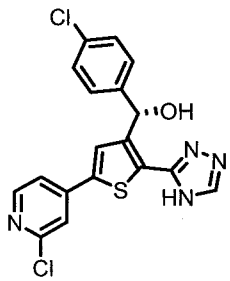
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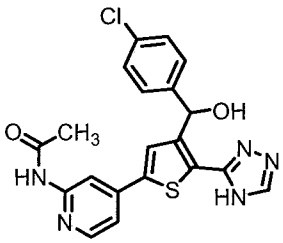
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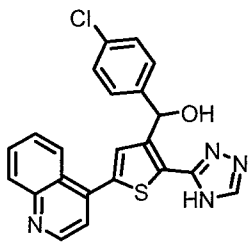
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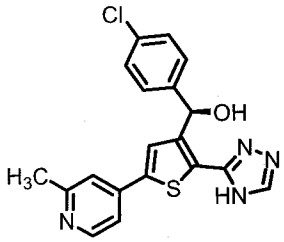
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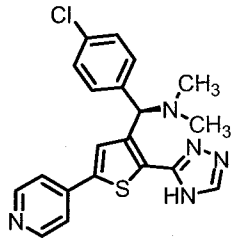
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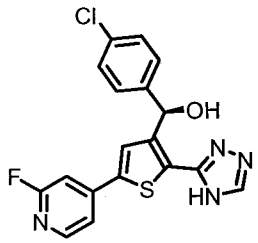
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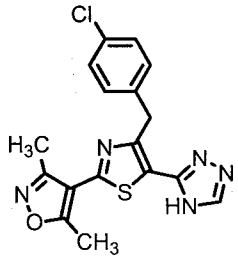
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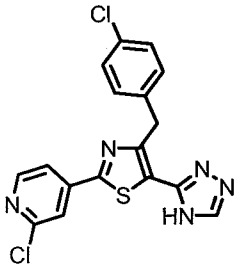
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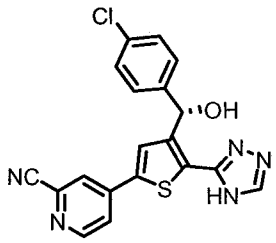
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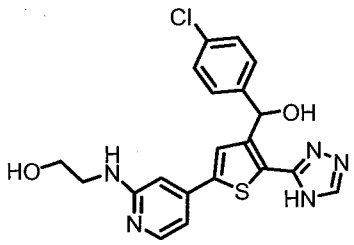
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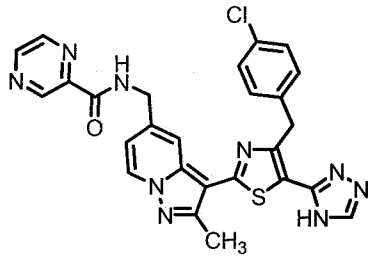
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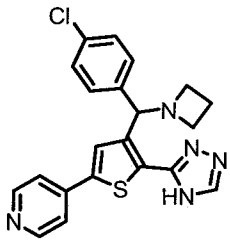
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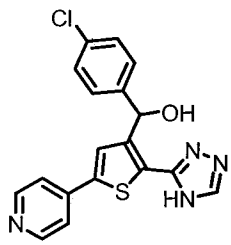
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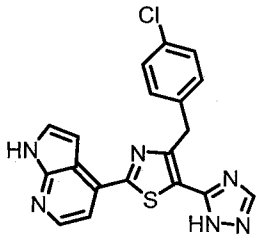
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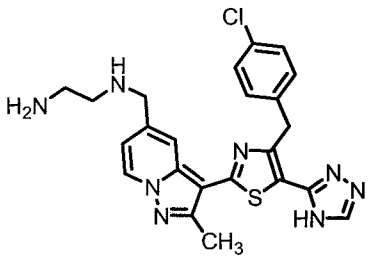
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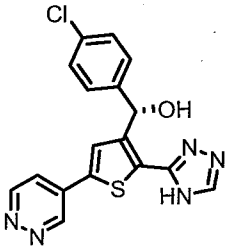
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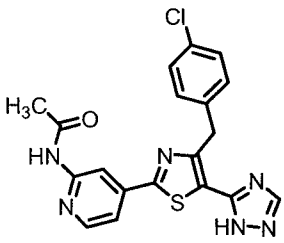
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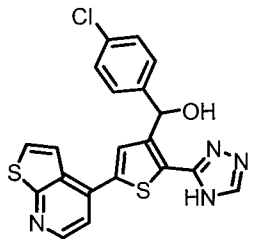
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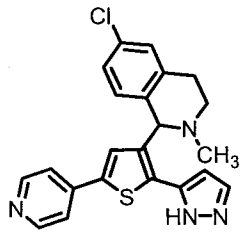
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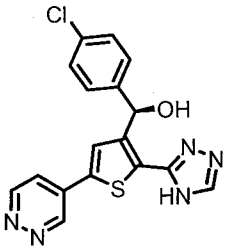
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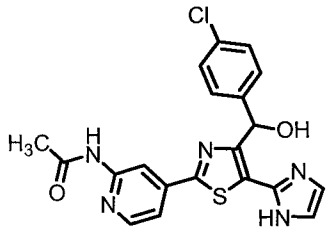
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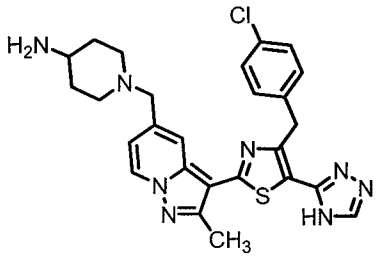
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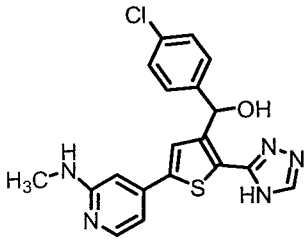
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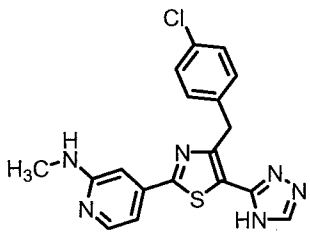
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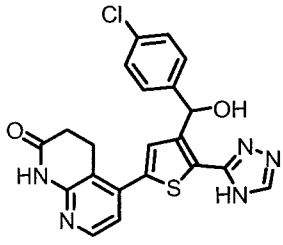
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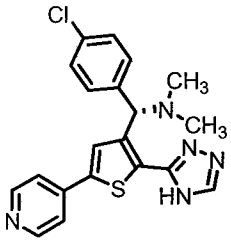
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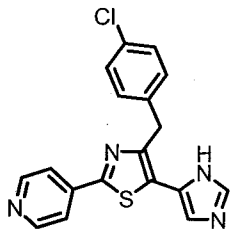
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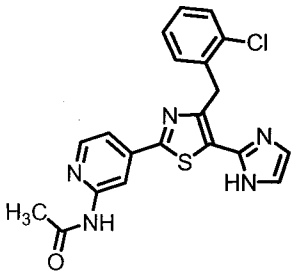
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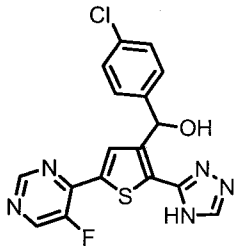
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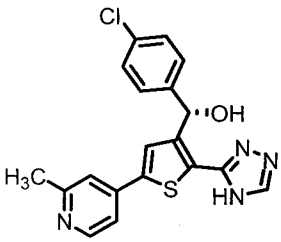
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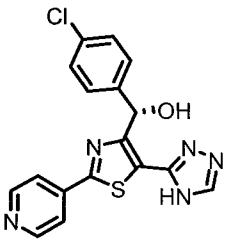
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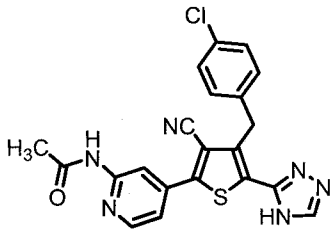
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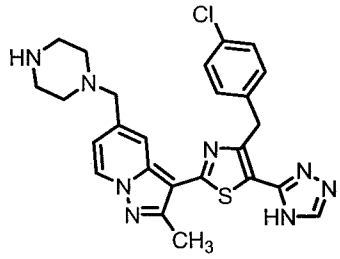
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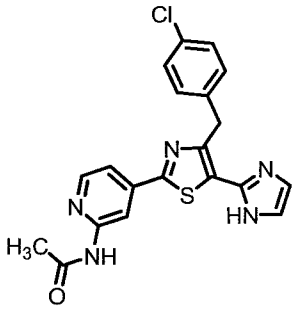
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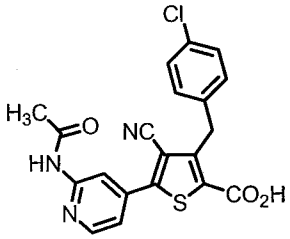
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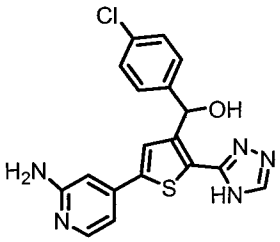
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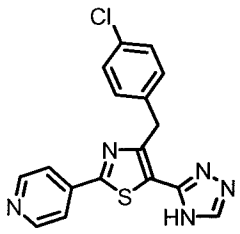
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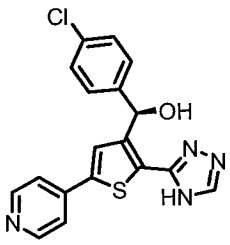
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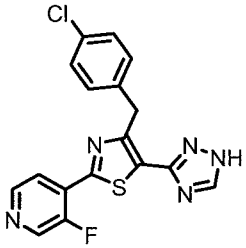
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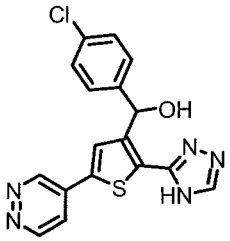
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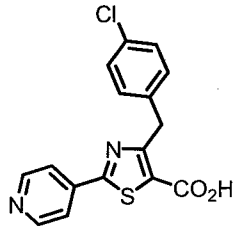
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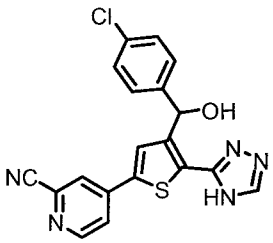
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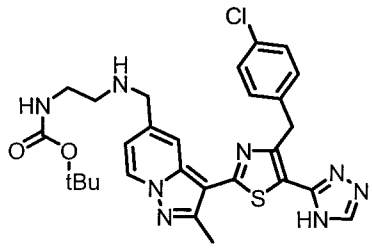
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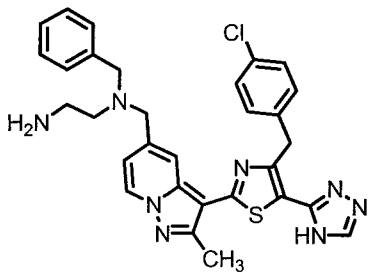
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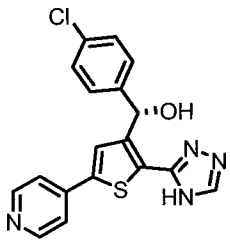
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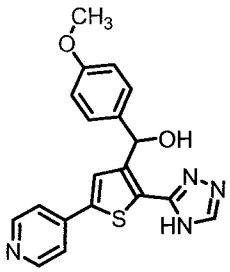
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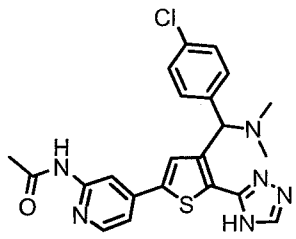
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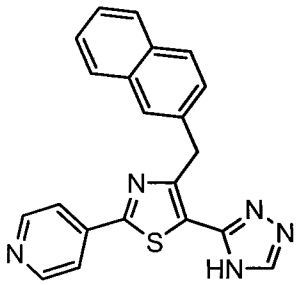
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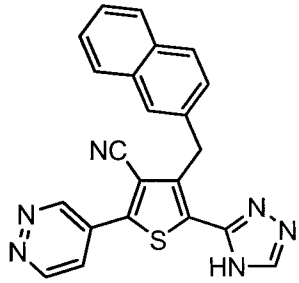
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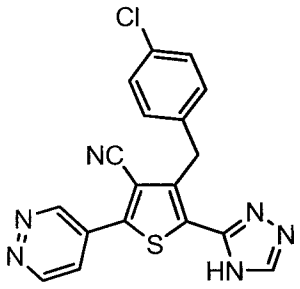
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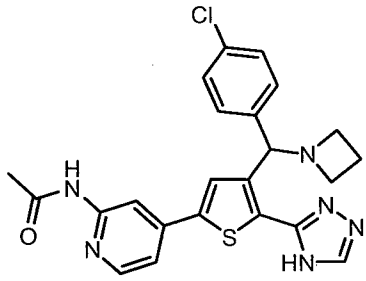
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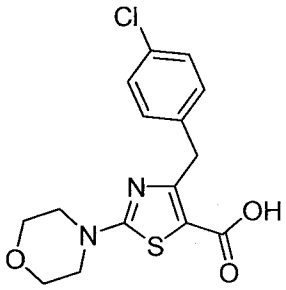
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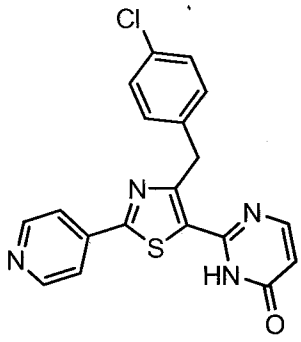
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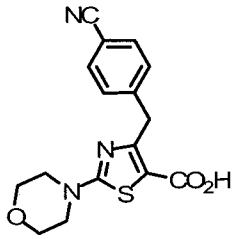
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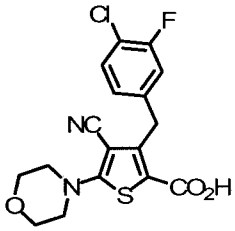
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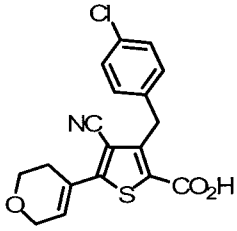
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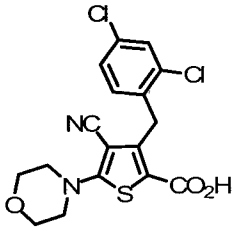
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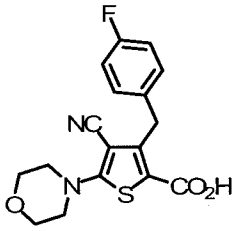
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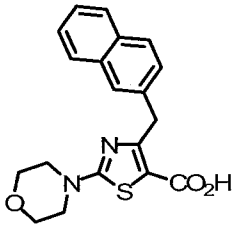
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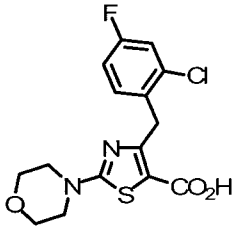
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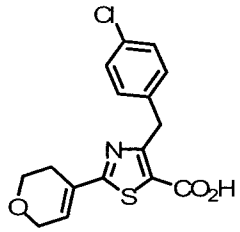
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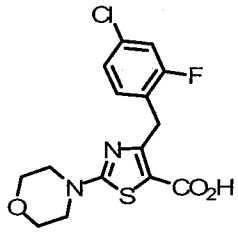
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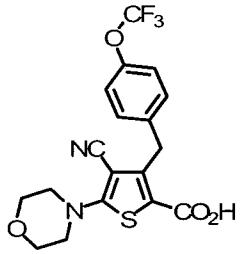
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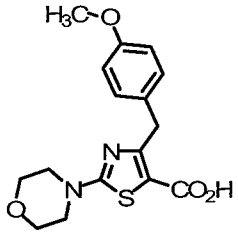
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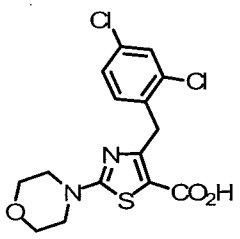
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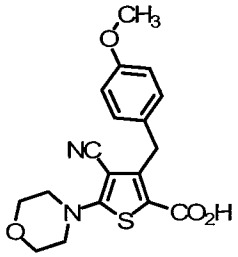
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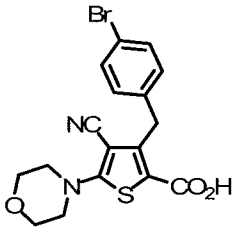
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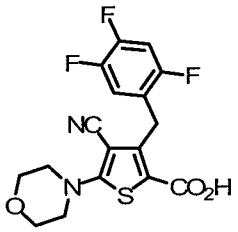
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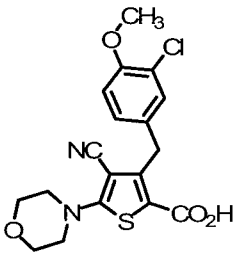
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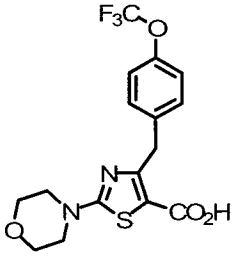


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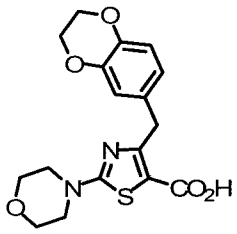


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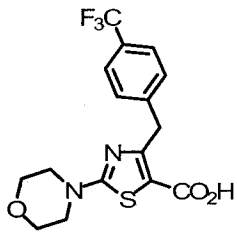




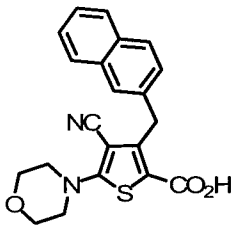
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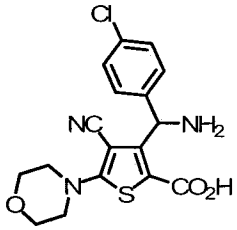
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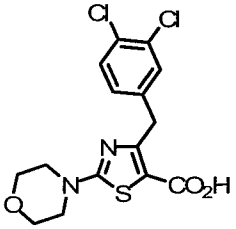
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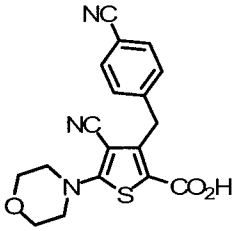
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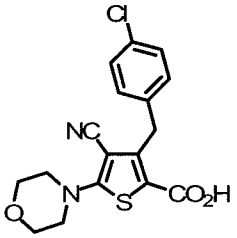
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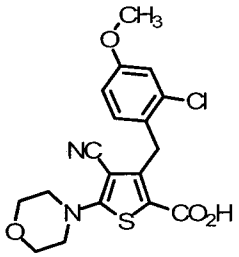
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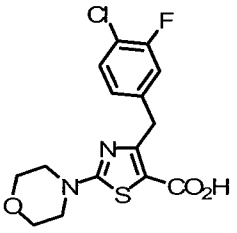


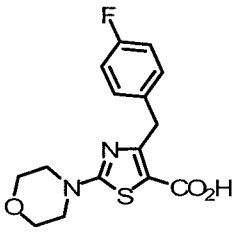
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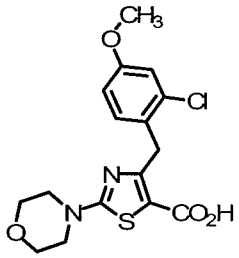
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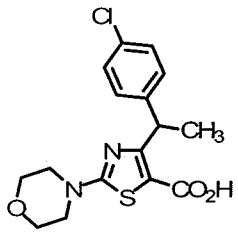




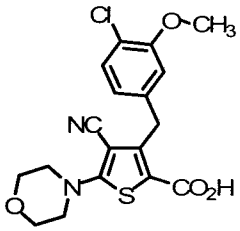
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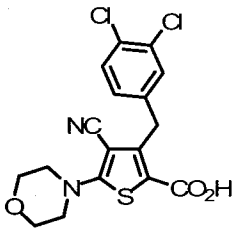
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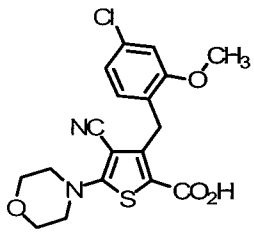
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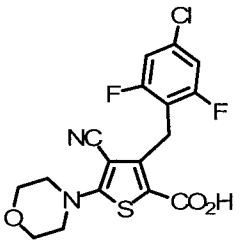
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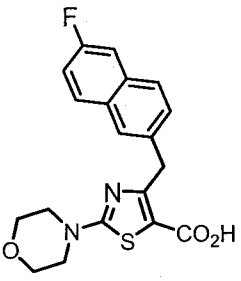


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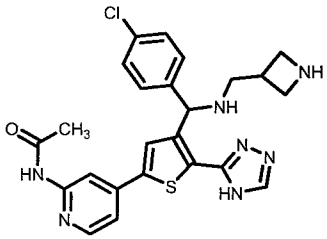


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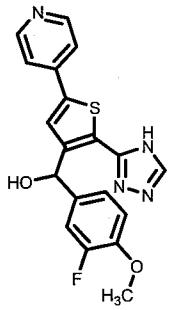




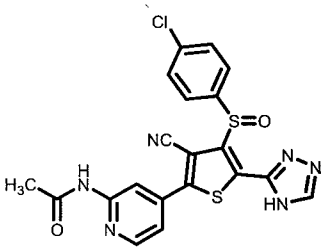
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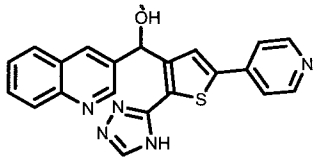
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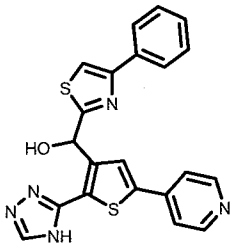
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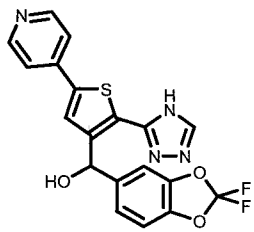
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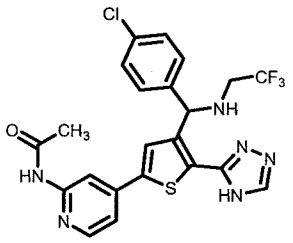
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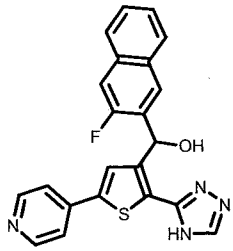
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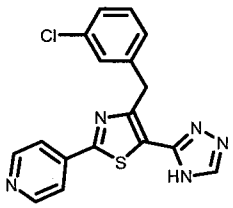
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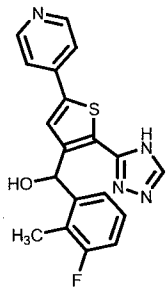
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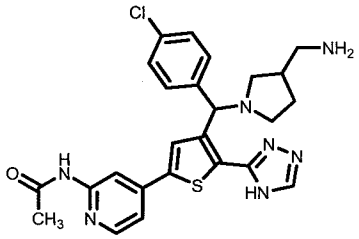
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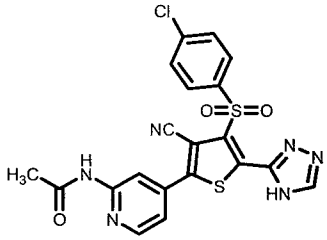
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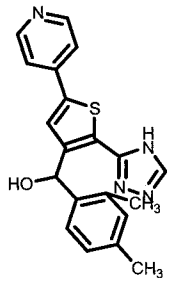
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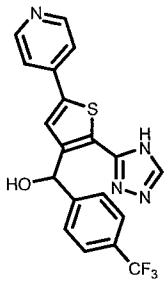
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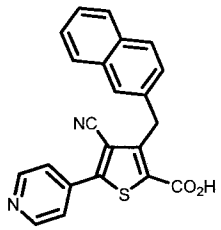
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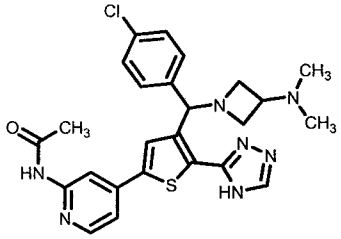
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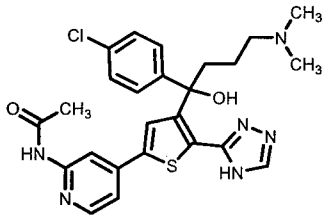
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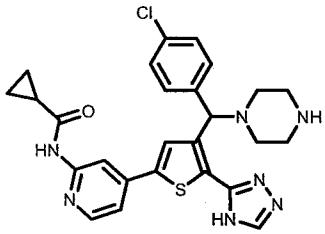
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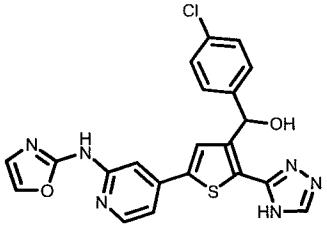
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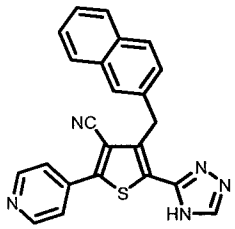
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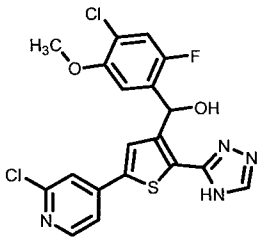
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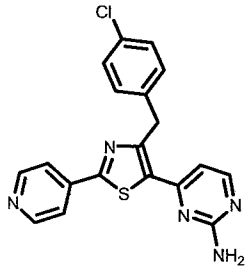
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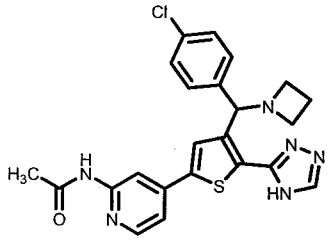
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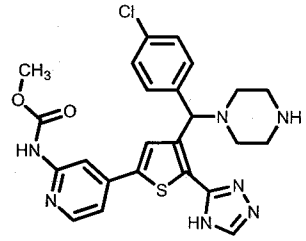
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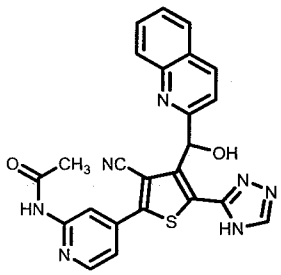
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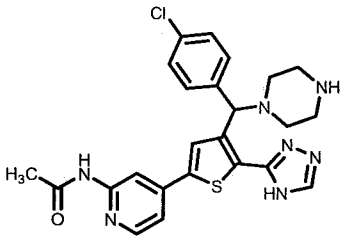
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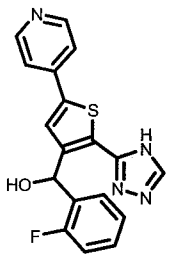
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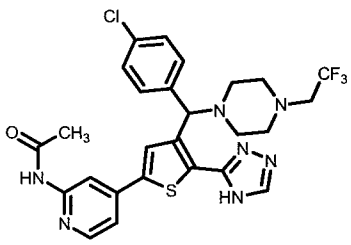
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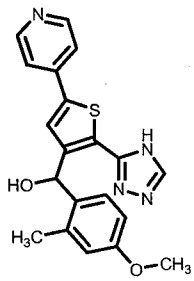
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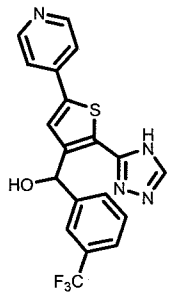
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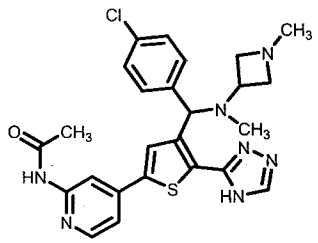
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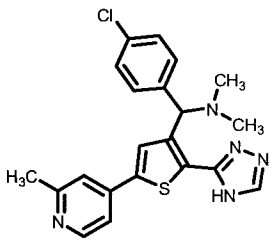
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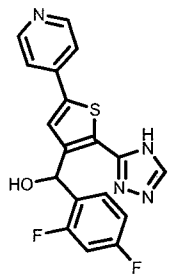
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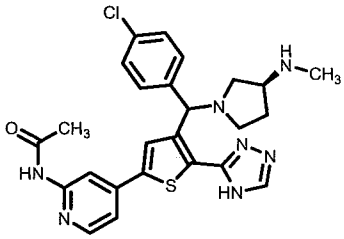
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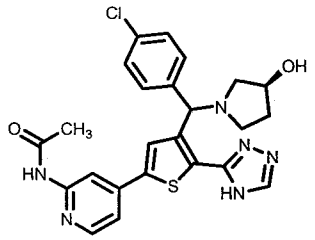
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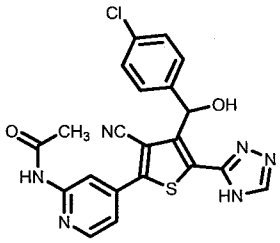
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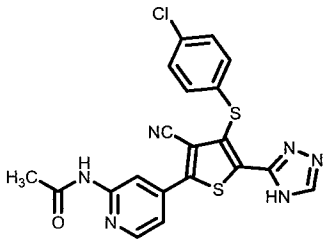
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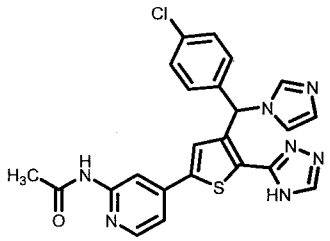
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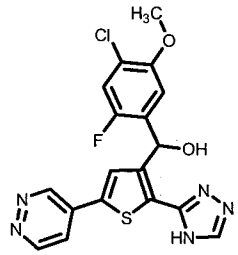
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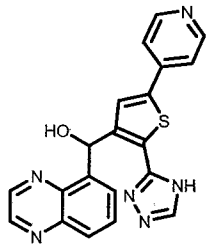
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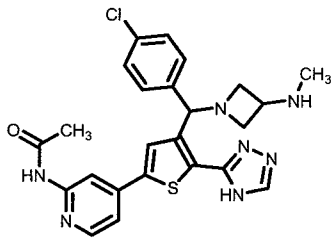
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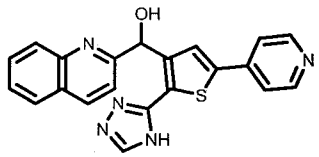
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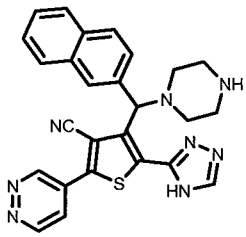
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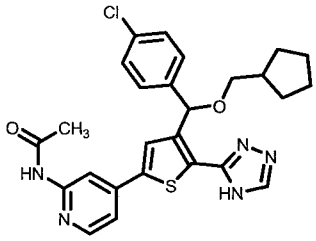
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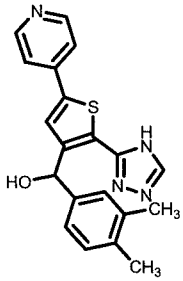
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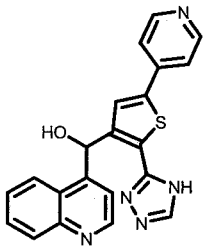
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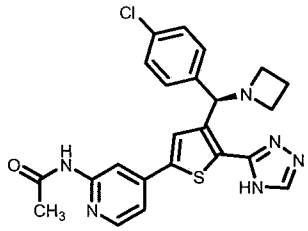
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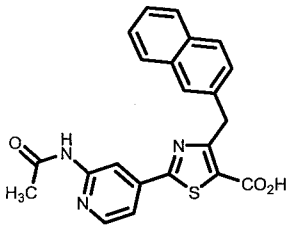
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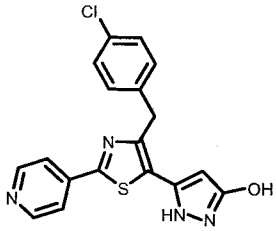
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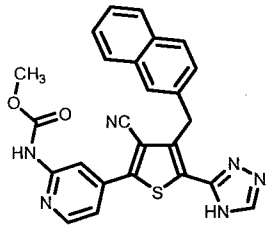
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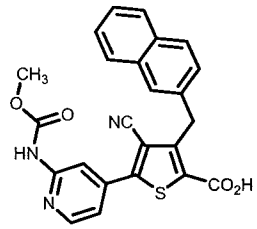
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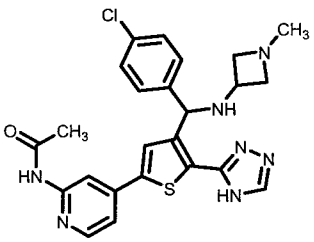
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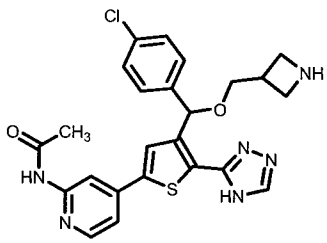
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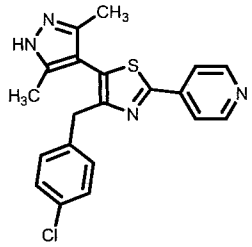
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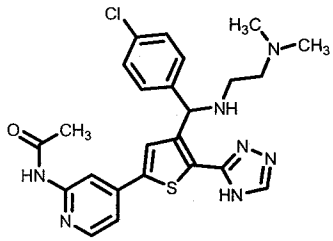
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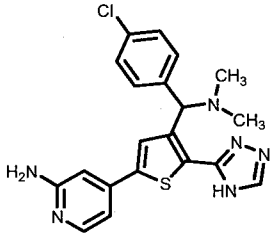
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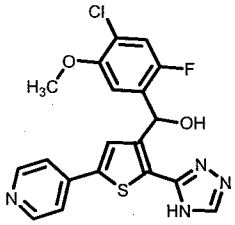
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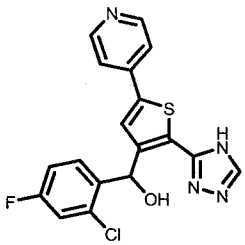
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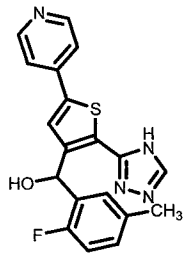
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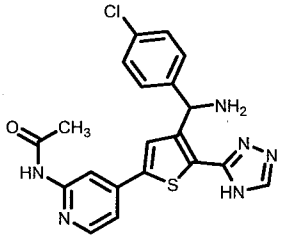
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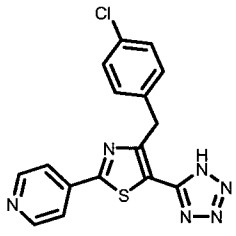
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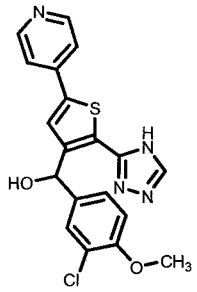
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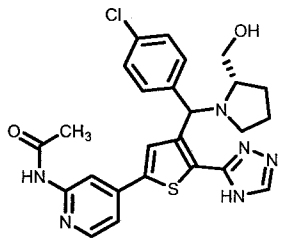
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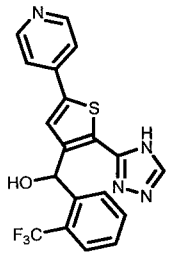
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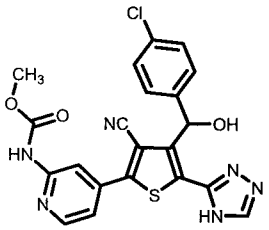
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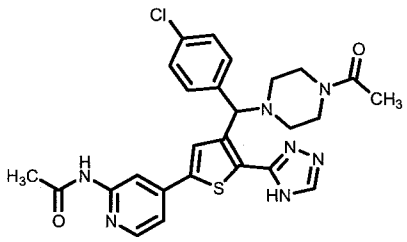
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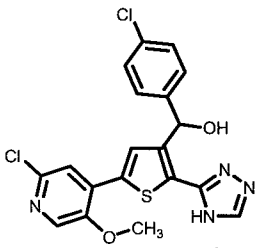
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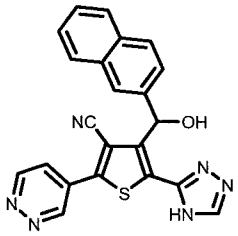
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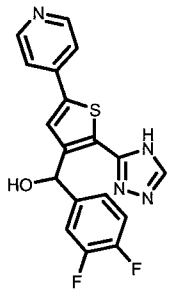
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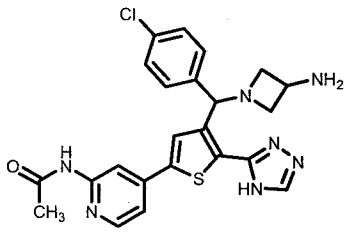
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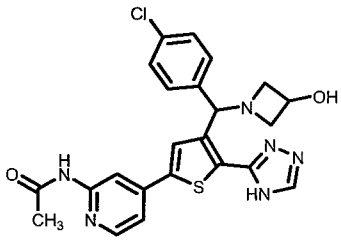
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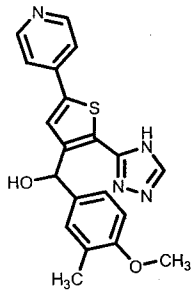
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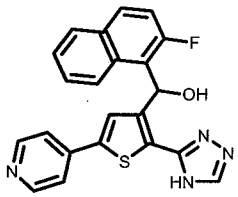
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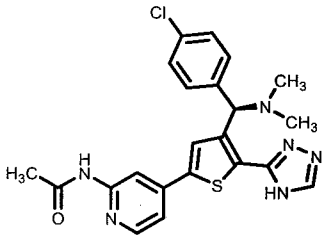
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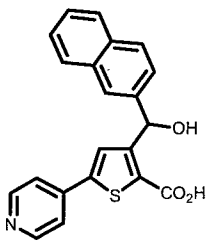
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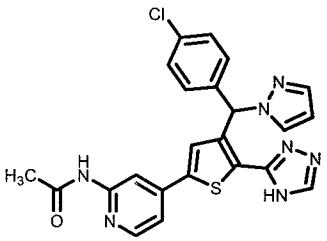
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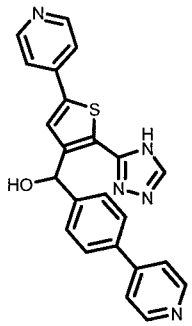
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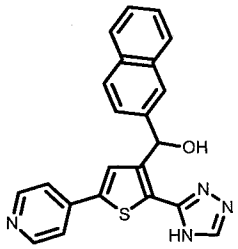
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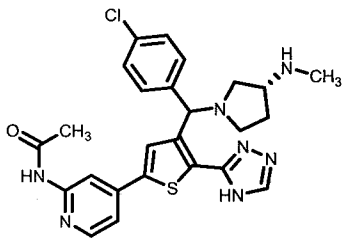
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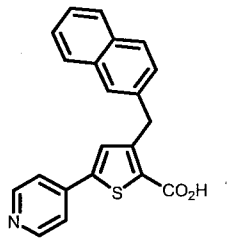
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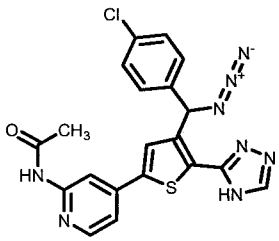
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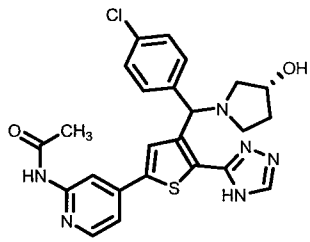
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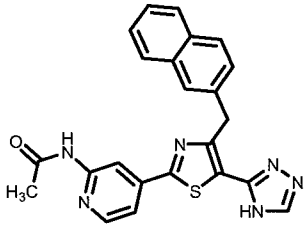
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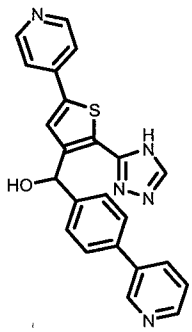
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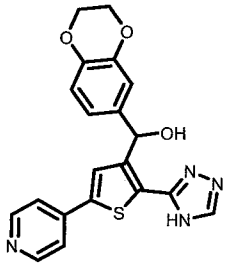
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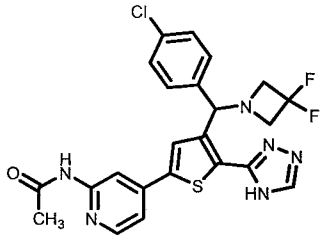
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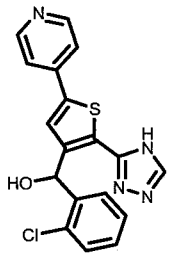
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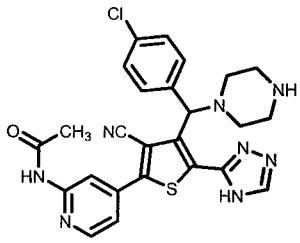
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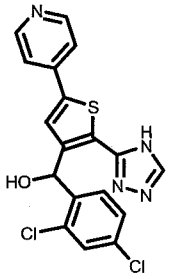
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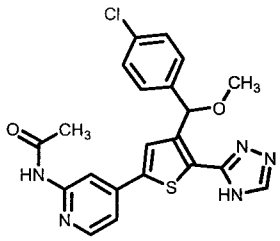
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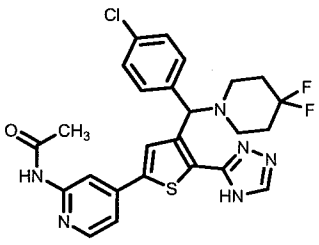
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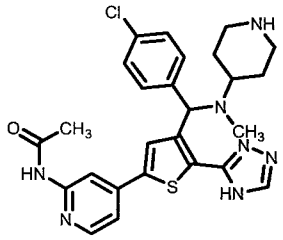
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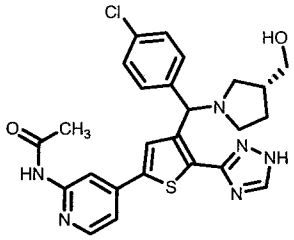
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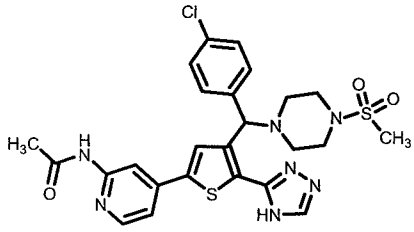
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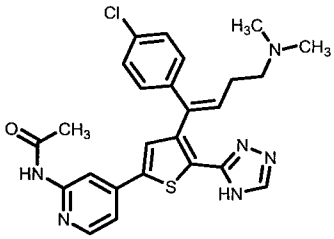
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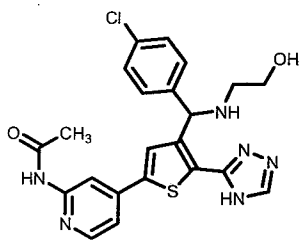
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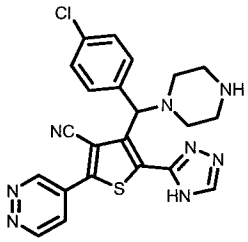
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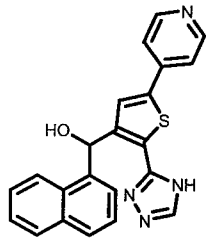
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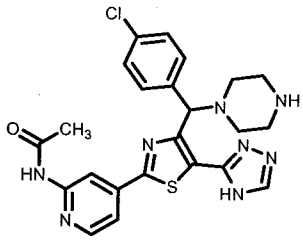
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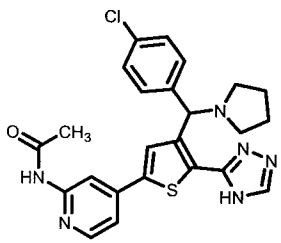
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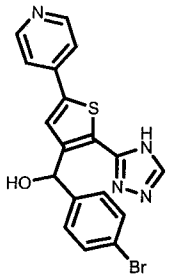
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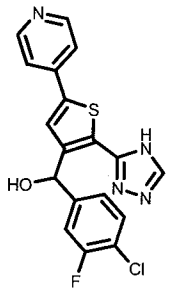
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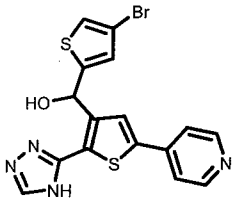
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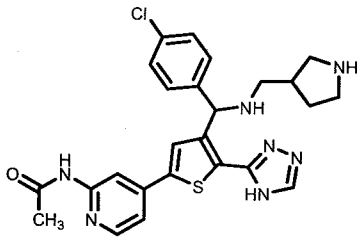
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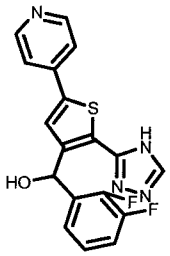
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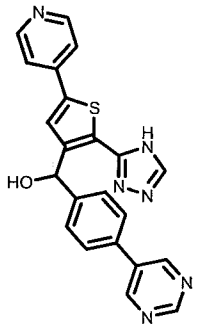
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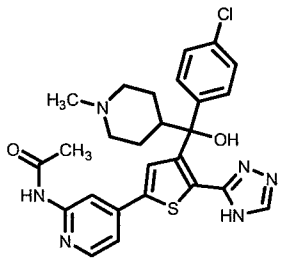
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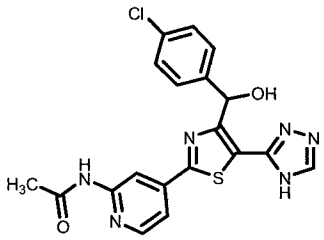
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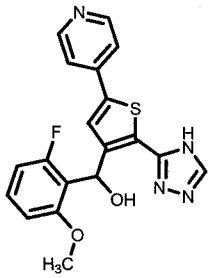
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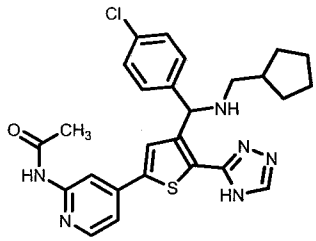
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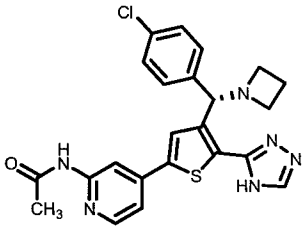
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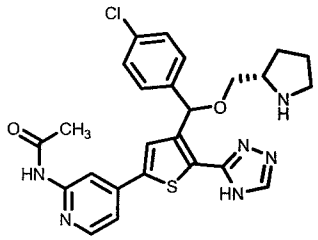
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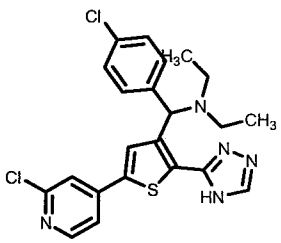
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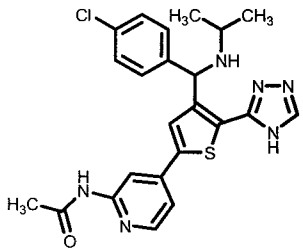
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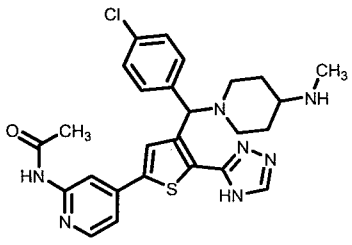
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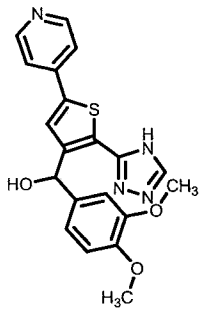
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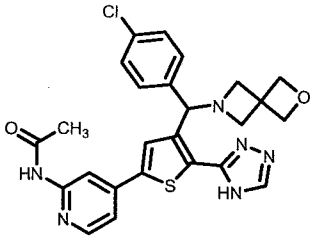
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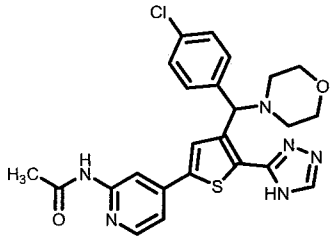
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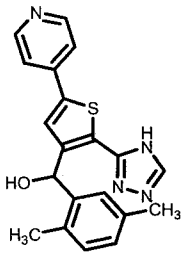
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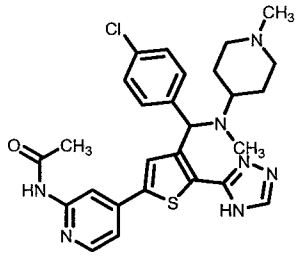
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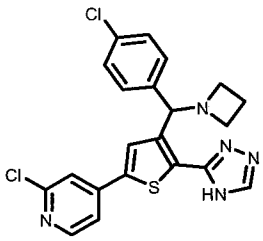
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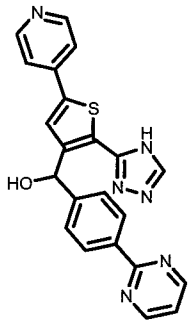
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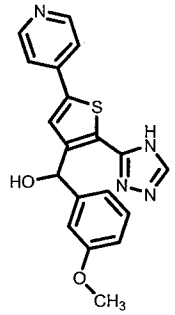
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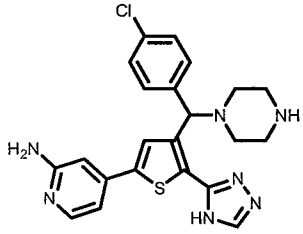
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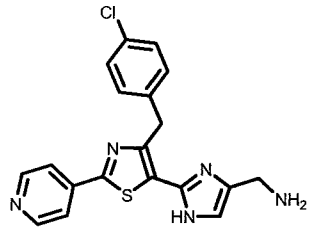
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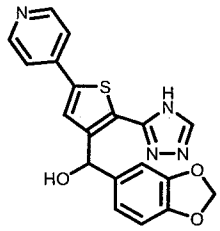
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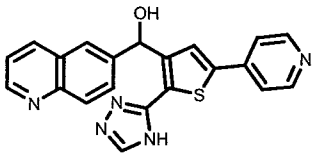
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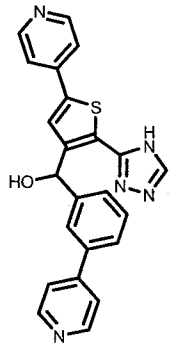
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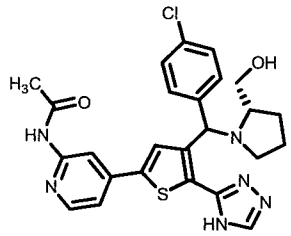
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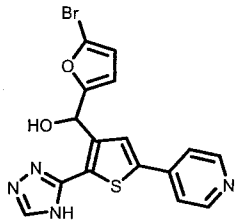
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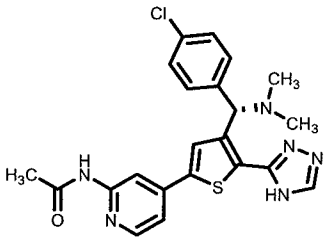
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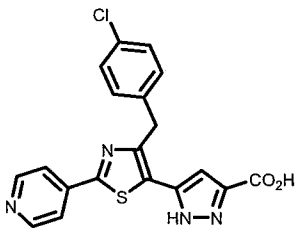
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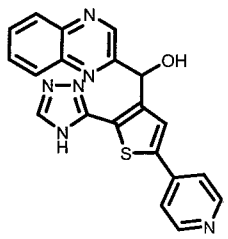
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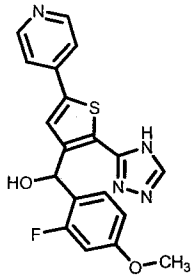
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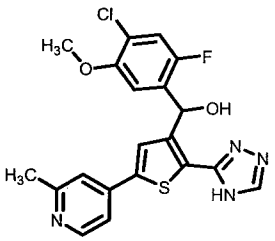
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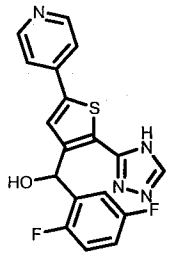
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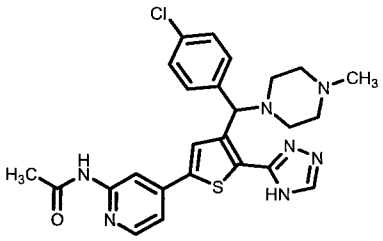
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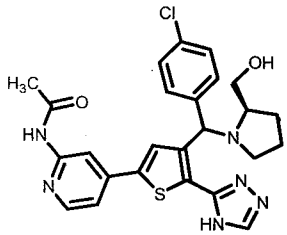
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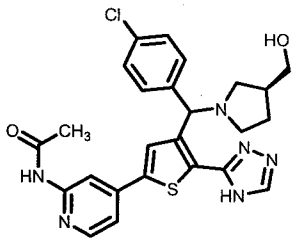
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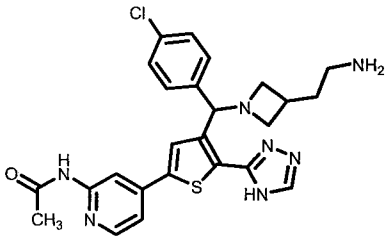
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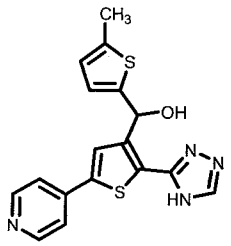
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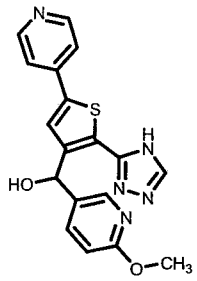
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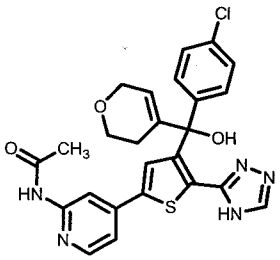
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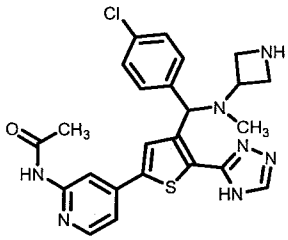
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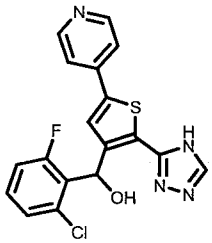
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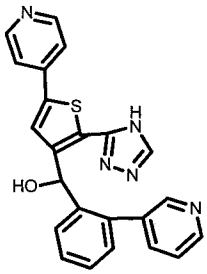
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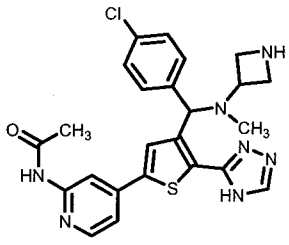
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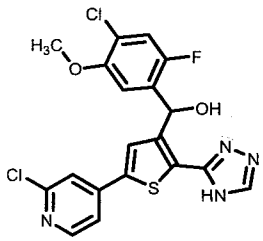
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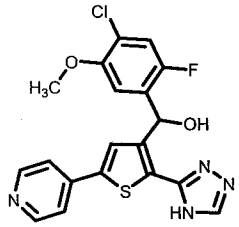
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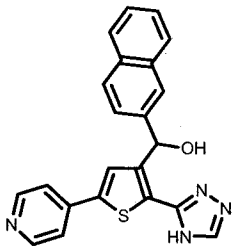
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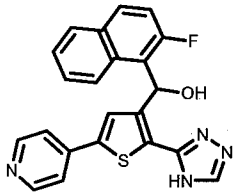
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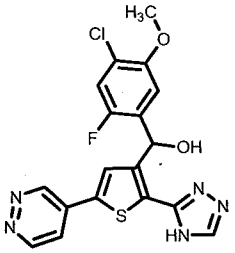
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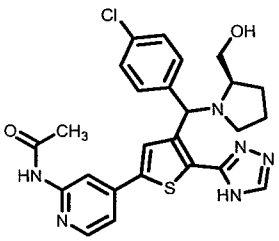
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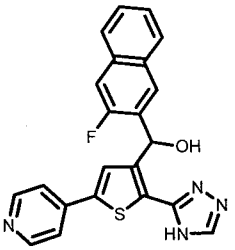
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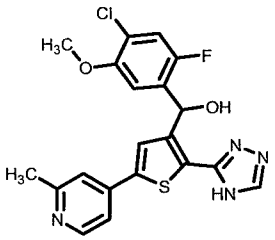
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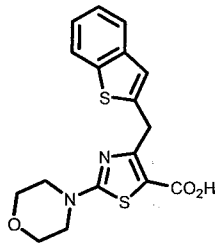
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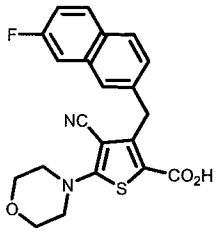
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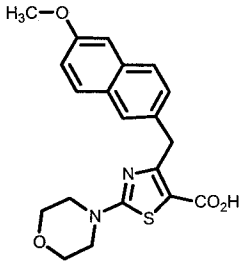
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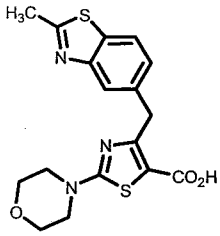
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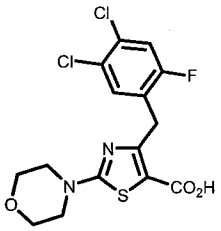
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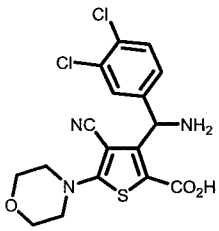
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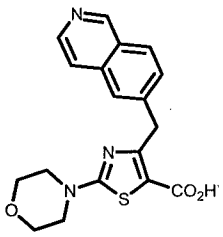
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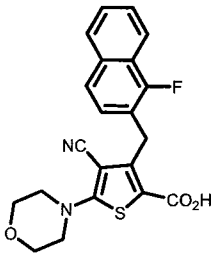
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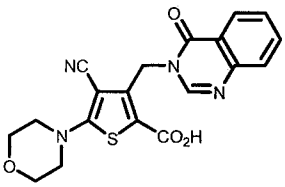
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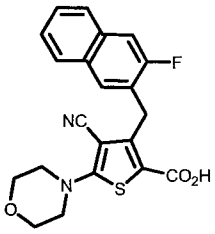
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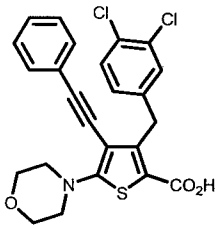
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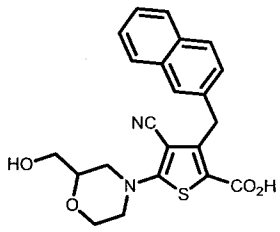
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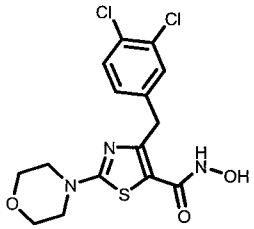
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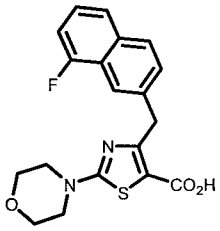
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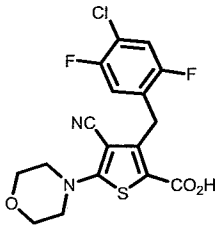
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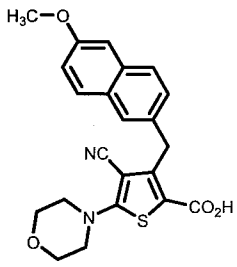
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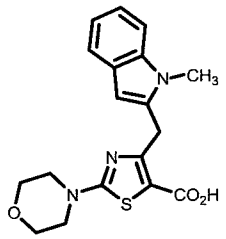
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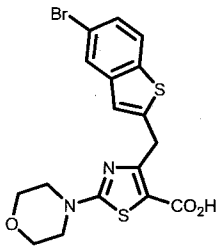
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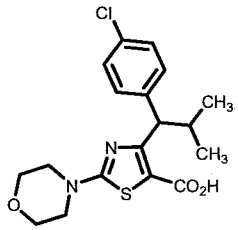
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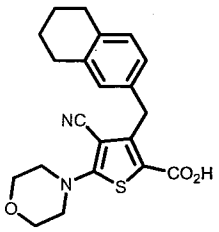
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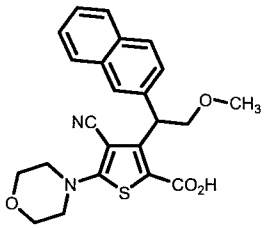
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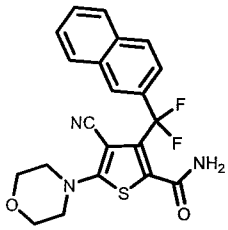
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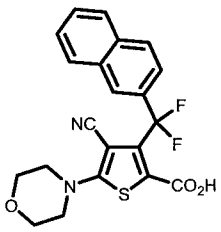
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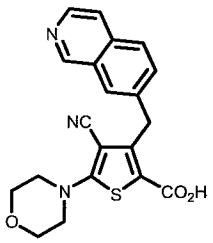
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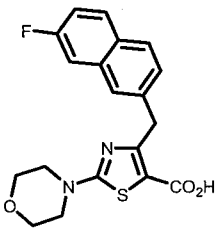
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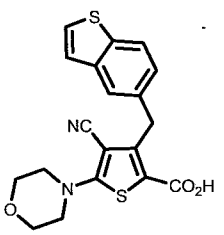
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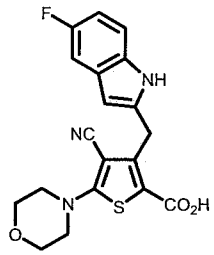
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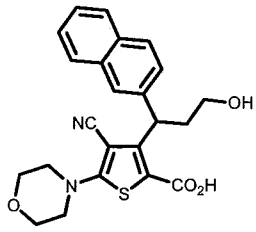
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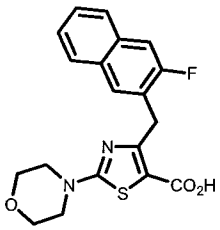
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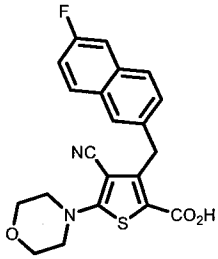
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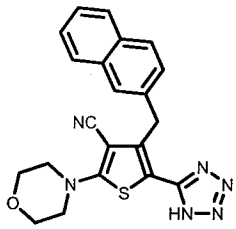
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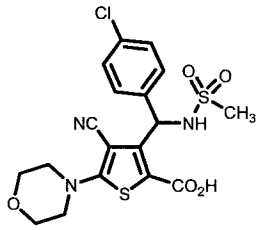
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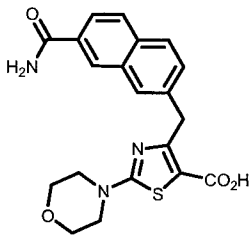
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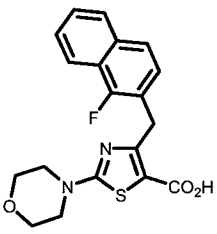
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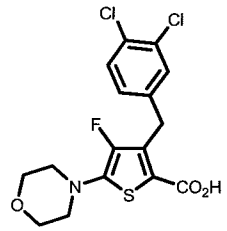
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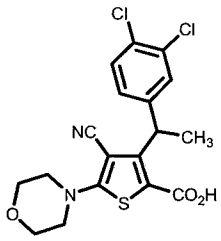
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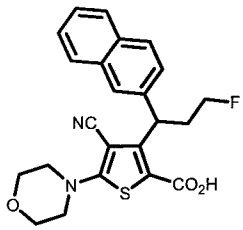
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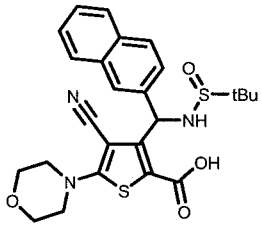
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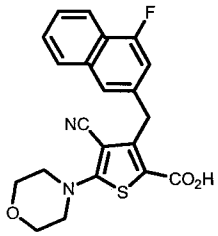
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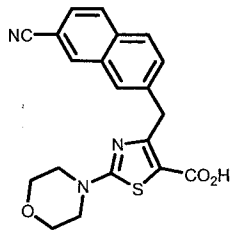
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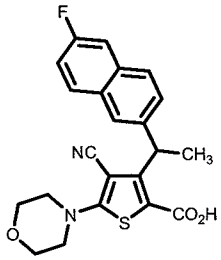
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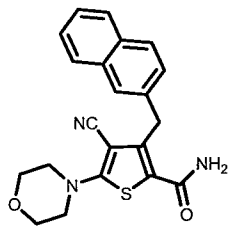
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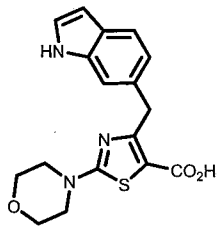
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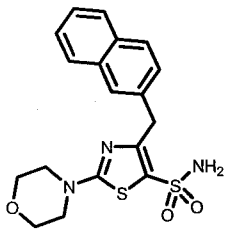
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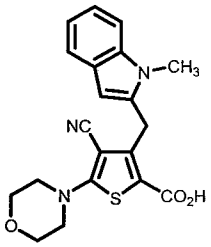
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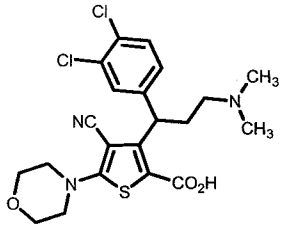
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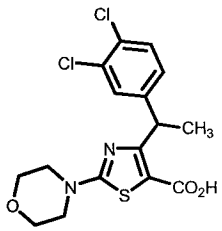
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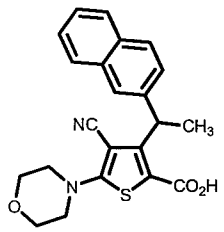
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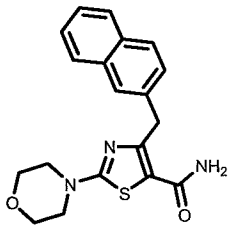
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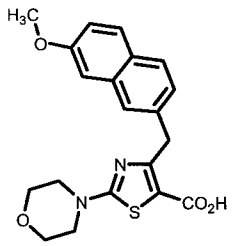
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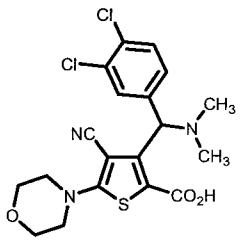
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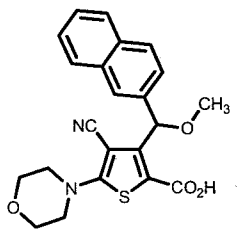
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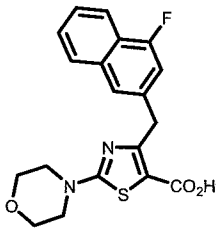
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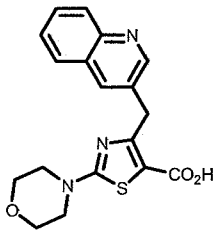
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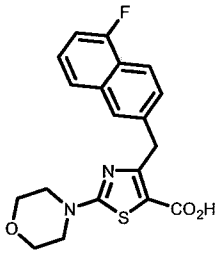
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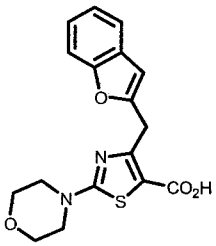
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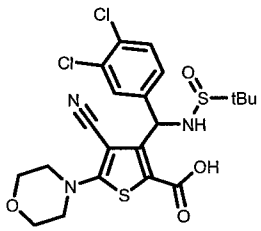
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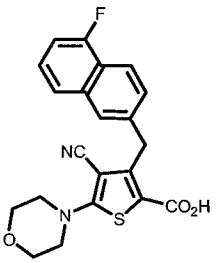
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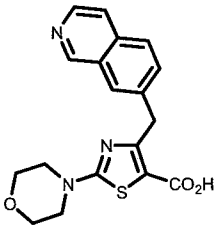
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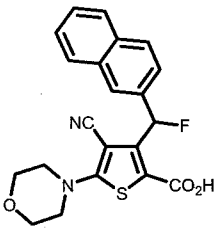
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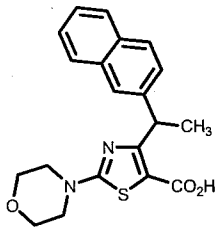
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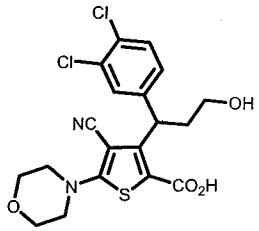
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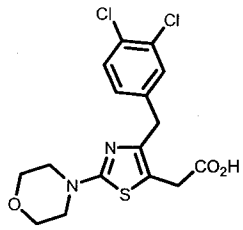
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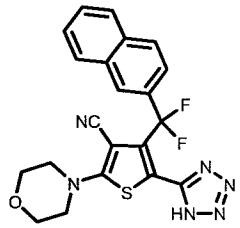
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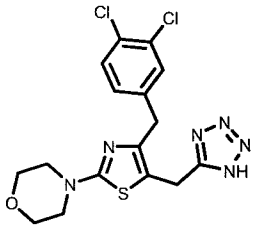
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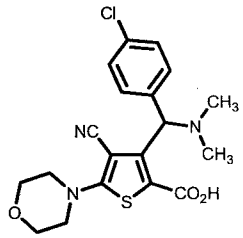
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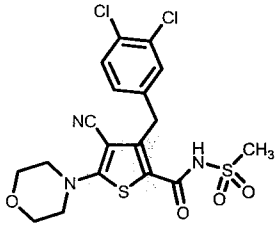
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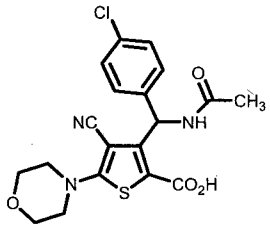
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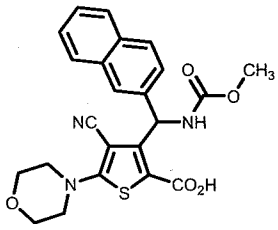
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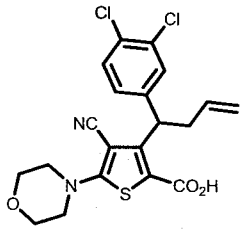
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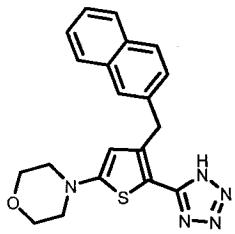
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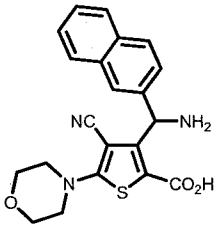
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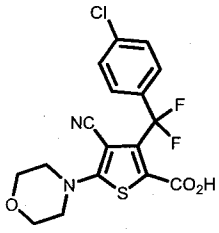
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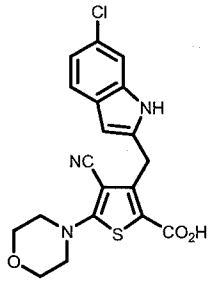
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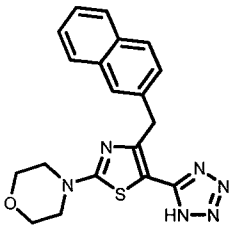
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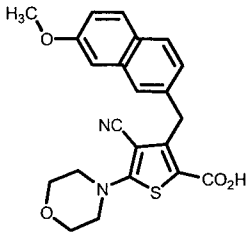
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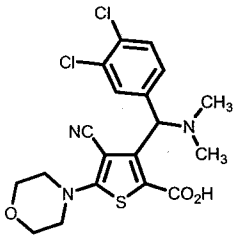
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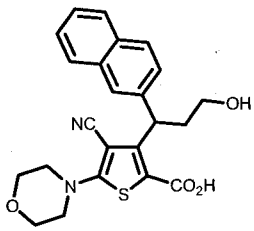
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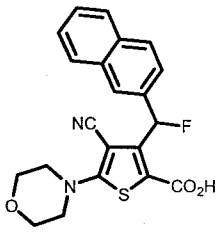
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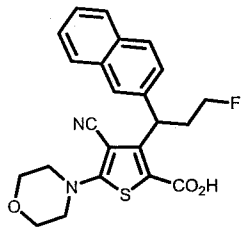
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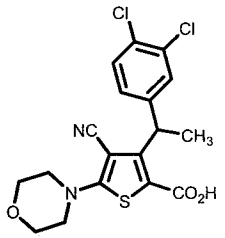
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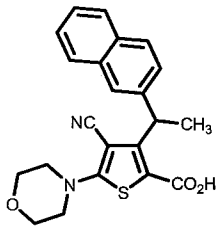
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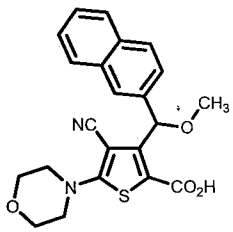
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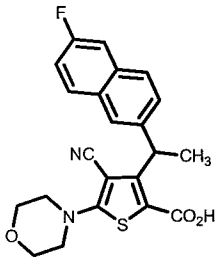
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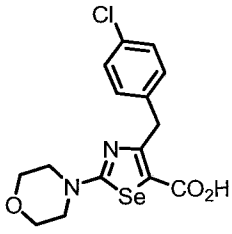
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[00392] Definitions

AcOH acetic acid

ACN acetonitrile

ATP adenosine triphosphate

br broad

BCA bicinchoninic acid

BSA bovine serum albumin

BOC tert-butoxycarbonyl

BuLi butyllithium

m-CPBA m-chloroperbenzoic acid

d doublet

dd doublet of doublets

DCE dichloroethane

DCM dichloromethane

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIPEA diisopropylethyl amine

DMAP *N,N*-dimethylaminopyridine

DME 1,2-Dimethoxyethane

DMEM Dulbecco's Modified Eagle's Medium

DMF N, N-dimethylformamide

DMF-DMA N, N-dimethylformamide dimethyl acetal

DMSO dimethylsulfoxide

DPPA diphenylphosphoryl azide

DTT dithiothreitol

dppf diphenylphosphinoferrocene

EDCI N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

EDTA ethylenediaminetetraacetic acid

EtOAc ethyl acetate

EtOH ethanol

FA formic acid

FBS fetal bovine serum

J coupling constant

h hours

Hz: hertz

HATU N, N, N', N'-tetramethyl-o-(7-azabenzotriazole-1-yl)uronium hexafluorophosphate

HBTU o-benzotriazol-1-yl-N, N, N', N'-tetramethyluronium hexafluorophosphate

HEPES N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)

HOBT 1-hydroxybenztriazole hydrate

HRMS high resolution mass spectrum

LAH lithium aluminum hydride

LCMS liquid chromatography mass spectrum

LDA lithium diisopropylamide

LiHMDS Lithium bis(trimethylsilyl)amide

m multiplet

m/z mass to charge

Me methyl

MeOH methanol

min minutes

MS mass spectrum

MTT methylthiazoletetrazolium

MWI microwave irradiation

NBS N-bromosuccinimide

PBS phosphate buffered saline

PKA cAMP-dependent protein kinase

rt room temperature

s singlet

t triplet

TEA triethylamine

TFA: trifluoroacetic acid

TFFA trifluoroacetic anhydride

THF tetrahydrofuran

TMB 3,3′,5,5′-Tetramethylbenzidine

TMEDA Tetramethylethylenediamine

q quartet

WST (4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-benzene disulfonate sodium salt)

[00393] The following analytical methods were used:

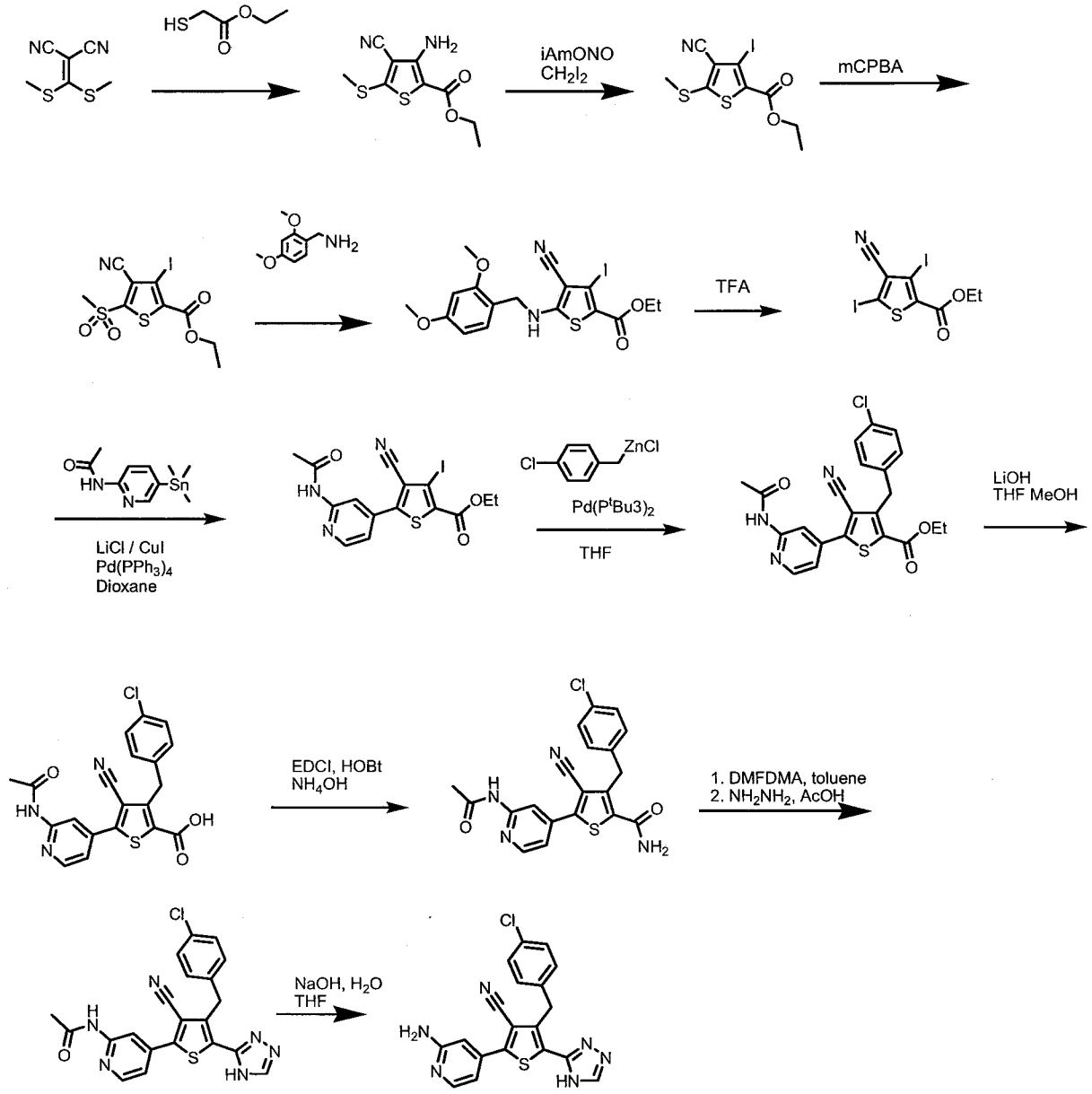
[00394] LCMS sectra were run on a Phenominex Luna 5μm C18 50 × 4.6 mm column on a Hewlett-Packard HP1100 using the following gradients:

- Method Formic Acid (FA): Acetonitrile containing 0 to 100 percent 0.1 % formic acid in water (2.5 ml/min for a 3 minute run).
- Method Ammonium Acetate (AA): Acetonitrile containing 0 to 100 percent 10 mM ammonium acetate in water (2.5 ml/min for a 3 minute run).

[00395] Chiral isomers were separated using chiral HPLC on a Chiralpak IC 250x25 mm 5 micron column using hexane/ethanol/diethylamine or hexane/isopropylalcohol/ethanol/diethylamine as mobil phase. Absolute configurations of the separated isomers were unknown, structures were assigned arbitrarily.

[00396] NMR spectrum is shown by proton NMR, with tetramethylsilane as the internal standard and using 300MHz Bruker Avance spectrometer equipped with a 5mm QNP probe and 400MHz Bruker Avance II spectrometer equipped with a 5mm QNP probe for the measurement; δ values are expressed in ppm.

[00397] Example 1: Synthesis of *N*-{4-[4-(4-chlorobenzyl)-3-cyano-5-(4*H*-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound 71) and 2-(2-aminopyridin-4-yl)-4-(4-chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)thiophene-3-carbonitrile (Compound 12)



[00398] **Step 1:** Ethyl 3-amino-4-cyano-5-(methylsulfanyl)thiophene-2-carboxylate

[00399] A mixture of [bis(methylsulfanyl)methylene]malononitrile (40 g, 230 mmol), ethylthioglycolate (29 g , 230 mmol) and TEA (24 mL, 173 mmol) in MeOH (600 mL) was allowed to stir at reflux for 2 h. The reaction mixture was allowed to cool overnight and the precipitate was filtered off then washed with cold MeOH (3x50 mL) to give ethyl 3-amino-4-cyano-5-(methylsulfanyl)thiophene-2-carboxylate (52.4 g, 99 %). LCMS: (FA) ES+ 275.

[00400] **Step 2:** Ethyl 4-cyano-3-iodo-5-(methylsulfanyl)thiophene-2-carboxylate

[00401] Ethyl 3-amino-4-cyano-5-(methylsulfanyl)thiophene-2-carboxylate (10 g, 41.3 mmol) was dissolved in acetonitrile (50 mL) under an atmosphere of argon. Diiodomethane (11.6 mL, 0.144 mol) was added and the mixture was heated at 40°C. Isoamyl nitrite (12.1g, 0.103 mol) was added and the reaction was allowed to cool to room temperature and stirred for 2 hours. The mixture was cooled down to 0°C, diluted with hexane (50 mL) and the precipitate was filtered off, washed with 10:1 hexane-acetonitrile mixture (10 mL), 3:1 hexane-ether (10 mL) and hexane (10 mL). The precipitate was dried to afford ethyl 4-cyano-3-iodo-5-(methylsulfanyl)thiophene-2-carboxylate (6.90 g, 45%). LCMS: (FA) ES+ 354. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.38 (q, 2H), 2.70 (s, 3H), 1.40 (t, 3H).

[00402] **Step 3:** Ethyl 4-cyano-3-iodo-5-(methylsulfonyl)thiophene-2-carboxylate

[00403] Ethyl 4-cyano-3-iodo-5-(methylsulfanyl)thiophene-2-carboxylate (7.2 g, 20.4 mmol) was dissolved in DCM (200 mL) and THF (100 mL) and m-CPBA (9.14 g, 40.8 mmol) was added. The reaction mixture was stired at rt overnight. Sodium sulfite (5.14 g, 40.8 mmol) was added and the mixture was stirred for 10 minutes followed by the addition of potassium carbonate (8.45, 61.2 mmol). The suspension was stirred at rt for 1 hour and filtered through celite, washed with DCM and the solvent was evaporated to afford ethyl 3-iodo-4-cyano-5-(methylsulfonyl)thiophene-2-carboxylate (6.80 g, 78%). LCMS: (FA) ES+ 386. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.45 (q, 2H), 3.38 (s, 3H), 1.43 (t, 3H).

[00404] **Step 4:** Ethyl 4-cyano-5-[(2,4-dimethoxybenzyl)amino]-3-iodothiophene-2-carboxylate

[00405] Ethyl 4-cyano-3-iodo-5-(methylsulfonyl)thiophene-2-carboxylate (5.60g, 0.0145mol) and 2,4-dimethoxybenzylamine (3.51 mL, 0.0234 mol) were combined in tetrahydrofuran (100 mL) and stirred at 60 °C for 3 days. The reaction was concentrated in vacuo, diluted with dichloromethane and hexanes and the resultant precipitate was filtered to yield the title compound (5.56, 81%) as a yellow solid. LCMS: (FA) ES^+, 473. ^{1}H NMR (400MHz, d_6-DMSO) δ: 9.05 (s, 1H) 7.10 (d, 1H, J = 8.57Hz), 6.60-6.50 (m, 2H), 4.30 (s, 2H), 4.22-4.14 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 1.26-1.21 (m, 3H).

[00406] **Step 5:** Ethyl 4-cyano-3,5-diiodothiophene-2-carboxylate

[00407] To a solution of ethyl 4-cyano-5-[(2,4-dimethoxybenzyl)amino]-3-iodothiophene-2-carboxylate (4.50 g, 9.53 mmol) in dichloromethane (100 mL) at room temperature was added trifluoroacetic acid (22.5 mL, 292 mmol). The mixture was then stirred at room temperature for 10 minutes. The solvent was evaporated and the excess trifluoroacetic acid was removed by azeotroping with toluene. The crude material was diluted with ethyl acetate, then treated with saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate five times and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield ethyl 5-amino-4-cyano-3-iodothiophene-2-carboxylate (2.85 g, 88%). LCMS: (FA) ES^+, 323. ^{1}H NMR (400MHz, d_6-DMSO) δ: 8.18 (s, 2H), 4.20-4.16 (m, 2H), 2.50-

2.48 (m, 3H). To a suspension of 5-amino-4-cyano-3-iodothiophene-2-carboxylate (2.85 g, 8.85 mmol) in acetonitrile (46.2 mL) under argon was added diiodomethane (2.49 mL, 31.0 mmol). The mixture was heated to 38°C for 30 minutes, then amyl nitrite (2.59 g, 22.1 mmol) was added dropwise over 5 minutes. The reaction was slowly allowed to cool to room temperature then the mixture was concentrated and column chromatography was performed to yield the title compound (3.20 g, 79%). LCMS: (FA) ES^+, 434. ^1H NMR (400MHz, d_6-DMSO) δ: 4.33-4.27 (m, 2H), 2.51-2.47 (m, 3H).

[00408] **Step 6:** Ethyl 5-[2-(acetylamino)pyridin-4-yl]-4-cyano-3-iodothiophene-2-carboxylate

[00409] To a solution of ethyl 4-cyano-3,5-diiodothiophene-2-carboxylate (0.473 g, 1.09 mmol) and N-[4-(trimethylstannyl)pyridin-2-yl]acetamide (0.392 g, 1.31 mmol) in dioxane (10.2 mL) was added lithium chloride (0.139 g, 3.28 mmol), copper(I) iodide (0.0624 g, 0.328 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.0947 g, 0.0819 mmol). The reaction flask was evacuated and backfilled with argon, then the solution was heated at 110°C for 2 hours. The mixture was cooled to room temperature and a mixture of dichloromethane and methanol was added until almost all solids had dissolved. The suspension was filtered through celite and the filtrate was evaporated. Column chromatography was performed to yield the title compound (0.312 g, 65%). LCMS: (FA) ES+ 442. ^1H NMR (400MHz, d_6-DMSO) δ: 8.54-8.49 (m, 2H), 8.31 (s, 1H), 4.38-4.32 (m, 2H), 2.13 (s, 3H), 1.36-1.29 (m, 3H).

[00410] **Step 7:** Ethyl 5-[2-(acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxylate

[00411] To a solution of ethyl 5-[2-(acetylamino)pyridin-4-yl]-4-cyano-3-iodothiophene-2-carboxylate (0.209 g, 0.474 mmol) in tetrahydrofuran (3.3 mL) was added 4-chlorobenzylzinc chloride (0.50M solution in tetrahydrofuran, 1.89 mL, 0.947 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.0182 g, 0.0355 mmol) under argon. The solution was stirred at 60°C for 3 hours. The reaction was allowed to cool to room temperature and then the solvent was evaporated in vacuo. Column chromatography was performed to yield the title compound (0.159 g, 76%). LCMS: (FA) ES^+, 440. ^1H NMR (400MHz, $CDCl_3$) δ: 8.66 (br s, 1 H), 8.60 (br s, 1H), 8.38 (d, J=5.27Hz ,1H), 7.51-7.47 (m, 1H), 7.33-7.23 (m, 4H), 4.51 (s, 2H), 4.39 (q, J=7.03Hz, 2H), 2.24 (s, 3H), 1.39 (t, J=7.03Hz, 3H).

[00412] **Step 8:** 5-[2-(Acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxylic acid

[00413] To a solution of ethyl 5-[2-(acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxylate (0.080 g, 0.18 mmol) in tetrahydrofuran (1.28 mL) and water (0.85 mL) was added lithium hydroxide (1.0M solution in water, 0.236 mL, 0.236 mmol). The reaction mixture was stirred at room temperature for 16 hours. The mixture was acidified to pH 6 using aqueous 1N HCl (0.300 mL). The

mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, and then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield the title compound (0.058 g, 78%). LCMS: (FA) ES^+, 412. ^1H NMR (400MHz, d_6-DMSO) δ: 10.72 (s, 1H), 8.46-8.41 (m, 2H), 7.42-7.39 (m, 1H), 7.36-7.32 (m, 4H) 4.53 (s, 2H), 2.11 (s, 3H).

[00414] **Step 9:** 5-[2-(Acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxamide

[00415] To a solution of 5-[2-(acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxylic acid (0.0710 g, 0.172 mmol) in dichloromethane (5.0 mL) was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.0991 g, 0.517 mmol) and 1-hydroxybenzotriazole hydrate (0.0528 g, 0.345 mmol). The solution was stirred at room temperature for 30 minutes, then added 33% ammonium hydroxide (33:67 ammonia:water, 0.298 mL, 3.45 mmol) was added. The solution was then stirred at room temperature for 16 hours, then the mixture was concentrated and column chromatography was performed to yield the title compound (0.031 g, 42%). LCMS: (FA) ES^+, 411. ^1H NMR (400MHz, d_6-DMSO) δ: 10.79 (s, 1H), 8.50-8.46 (m, 2H), 8.14 (br s, 1H), 7.85 (br s, 1H), 7.47-7.43 (m, 1H), 7.39-7.34 (m, 2H), 7.29-7.24 (m, 2H), 4.41 (s, 2H), 2.12 (s, 3H).

[00416] **Step 10:** *N*-{4-[4-(4-chlorobenzyl)-3-cyano-5-(4*H*-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound **71**)

[00417] To a solution of 5-[2-(acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxamide (0.030 g, 0.073 mmol) in toluene (0.75 mL) was added 1,1-dimethoxy-N,N-dimethylmethanamine (0.0970 mL, 0.730 mmol), and the mixture was stirred at 100°C for 90 minutes. The mixture was concentrated and the residue was dissolved in acetic acid (0.75 mL). Hydrazine (0.0114 mL, 0.365 mmol) was added and the mixture was stirred at 100°C for 1 hour. The mixture was concentrated and the residue was treated with water. The precipitate was collected, washed with water and dried in a vacuum oven to yield the title compound (0.016 g, 48%). LCMS: (FA) ES^+, 435. ^1H NMR (400MHz, d_6-DMSO) δ: 10.76 (s, 1H), 8.77 (s, 1H), 8.54-8.46 (m, 2H), 7.50-7.47 (m, 1H), 7.37-7.26 (m, 4H), 4.63 (s, 2H), 2.12 (s, 3H).

[00418] **Step 11:** 2-(2-Aminopyridin-4-yl)-4-(4-chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)thiophene-3-carbonitrile (Compound **12**)

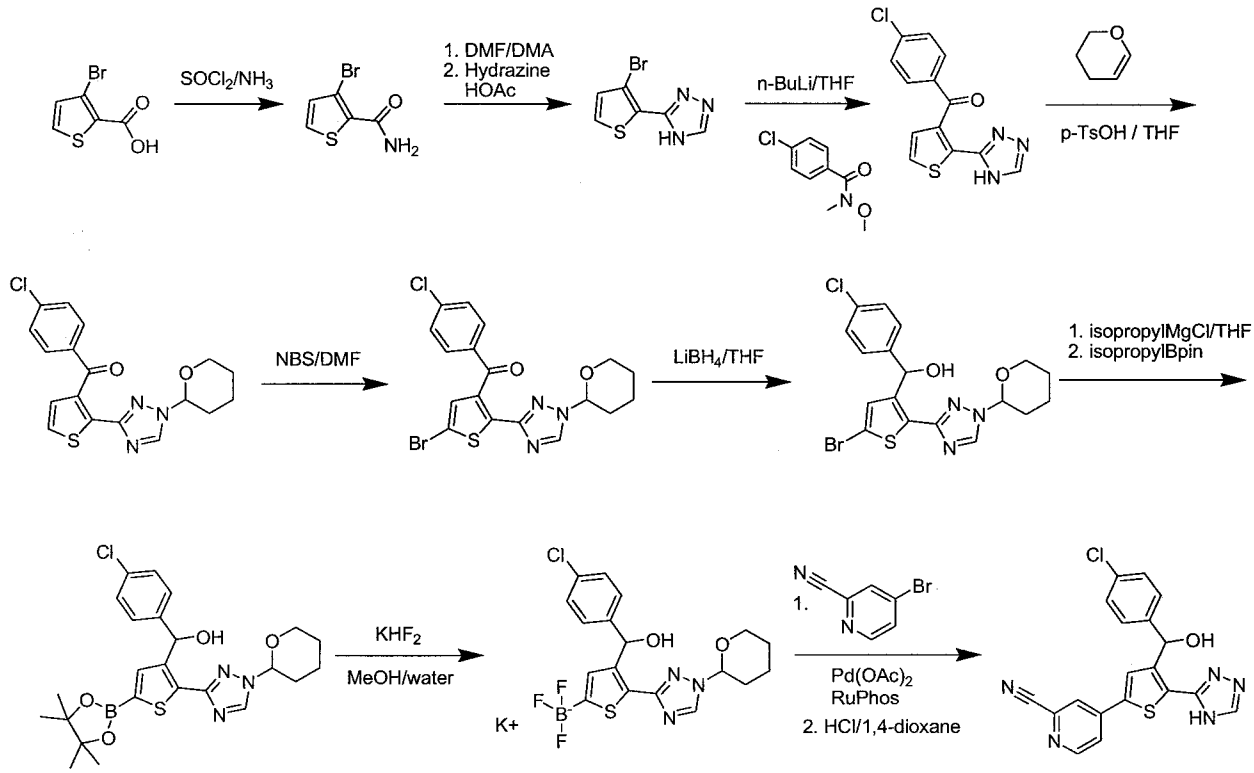
[00419] To a solution of *N*-{4-[4-(4-chlorobenzyl)-3-cyano-5-(4*H*-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (0.020 g, 0.046 mmol) in tetrahydrofuran (5.0 mL) was added sodium hydroxide (1.0M solution in water, 2.0 mL, 2.0 mmol). The solution was stirred at room temperature for 48 hours. The mixture was extracted with ethyl acetate three times, and the combined organic extracts

were then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield the title compound (0.007 g, 30%). LCMS: (FA) ES^+, 393. ^1H NMR (400MHz, d_6-DMSO) δ: 8.75 (s, 1H), 8.07-8.03 (m, 1H), 7.36-7.26 (m, 4H), 6.83-6.79 (m, 1H), 6.78-6.76 (m, 1H), 6.34-6.29 (m, 1H), 4.61 (s, 2H), 4.04 (s, 2H).

[00420] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 1:

36	LCMS: (FA) ES+ 355, 357
74	LCMS: (FA) ES+, 412, 414.
143	LC/MS: (FA) ES+ 371; ES- 369
148	LCMS: (FA) ES+ 394
179	LC/MS: (FA) ES+ 467
180	LC/MS: (FA) ES+ 444; ES- 442

[00421] Example 2 : Synthesis of 4-(4-((4-chlorophenyl)(hydroxy)methyl)-5-(4H-1,2,4-triazol-3-yl)thiophen-2-yl)picolinonitrile (Compound 81)



[00422] Step 1: 3-Bromothiophene-2-carboxamide

[00423] 3-Bromothiophene-2-carboxylic acid (63.61 g, 307.2 mmol) was weighed into a 1L round bottom flask equipped with reflux condenser and the flask was purged with argon. To this flask was added toluene (636.1 mL, 5972 mmol) and thionyl chloride (44.82 mL, 614.4 mmol) at room temperature, and the resulting mixture was stirred for 3h at 100°C. The reaction mixture was evaporated and the residue was azeotroped with toluene (2 x 100 mL). The resulting residue was dissolved in tetrahydrofuran (954.1 mL, 11760 mmol) then 10 M ammonia in water (170 mL, 2500 mmol) was added slowly into the solution. The mixture was stirred for 5h at room temperature. Thin-layer chromatography showed complete reaction. The reaction mixture was rotovaped to remove THF and the solid residue in water was filtered through a glass frit funnel then washed with water and dried under vacuum to give 3-bromothiophene-2-carboxamide as a white solid (33.26g, 52.5%). LCMS: (FA) ES+ 206.0, 208.0

[00424] **Step 2:** 3-(3-Bromothiophen-2-yl)-4H-1,2,4-triazole

[00425] 3-Bromothiophene-2-carboxamide (33.2 g, 161 mmol) in 1,1-dimethoxy-N,N-dimethylmethanamine (100 mL, 800 mmol) and toluene (100 mL, 900 mmol) was heated at 90 °C for 2h. The solvent was evaporated off and the residue was dissolved in acetic acid (183 mL, 3220 mmol). Hydrazine (20 mL, 600 mmol) was added and the mixture was heated at 90°C again. After 40min, LCMS showed complete reaction. The reaction mixture was evaporated to remove most of the acetic acid. Water was added and the precipitate was collected and dried in air overnight to afford 3-(3-bromothiophen-2-yl)-4H-1,2,4-triazole as a white powder(31.7g, 85.6%). LCMS: (FA) ES+ 230.0, 232.0

[00426] **Step 3:** (4-Chlorophenyl)[2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanone

[00427] To a solution of 3-(3-bromo-2-thienyl)-4H-1,2,4-triazole (15.05 g, 65.41 mmol) in Tetrahydrofuran (500 mL, 6000 mmol) was added dropwise 2.5M BuLi in hexanes (104 mL, 262 mmol) at -70°C (internal temperature) and the solution was stirred for 30 min at -78°C. A solution of 4-chloro-N-methoxy-N-methylbenzamide (41.24 g, 206.6 mmol) in tetrahydrofuran (80 mL, 1000 mmol) was then added dropwise into the suspension. The resulting mixture was stirred for 60 min at -78°C. Ammonium chloride (17.49 g, 327.0 mmol) in water (100 mL, 6000 mmol) was added to the mixture at -78°C and the mixture was stirred for 15min before being warmed to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, and then filtered to remove drying agent. The solvent was evaporated and the residue was purified by chromatography to afford (4-chlorophenyl)[2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanone as white solid (16.8g, 88.5%). LCMS: (FA) ES+ 289.9, 291.8

[00428] **Step 4:** (4-Chlorophenyl)(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)methanone

[00429] In a 500 mL, round bottomed flask, (4-chlorophenyl)[2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanone (16.89 g, 58.29 mmol) was dissolved in tetrahydrofuran (500.0 mL, 6164 mmol). To

the solution were added dihydropyran (31.9 mL, 3.50E2 mmol) and p-toluenesulfonic acid monohydrate (16.6 g, 87.4 mmol). The mixture was stirred for 3h at rt. The reaction was quenched by the addition of saturated aqueous solution of sodium bicarbonate (200 mL). The aqueous phase was separated and then extracted with EtOAc (300 mL). The combined organic phases were dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography to afford (4-chlorophenyl)(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)methanone as an oil which was dried under high vacuum overnight (19.4, 89.1%). LCMS: (FA) ES+ 374.2, 376.1.

[00430] **Step 5:** (5-Bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)(4-chlorophenyl)methanone

[00431] To a mixture of (4-chlorophenyl){2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}methanone (20.2 g, 54.0 mmol) in N,N-dimethylformamide (350 mL, 4500 mmol) was added dropwise a solution of N-bromosuccinimide (14.42 g, 81.05 mmol) in N,N-dimethylformamide (50 mL, 600 mmol) under argon. The mixture was stirred at rt with care taken to block the reaction from exposure to ambient light. After 3h reaction, LCMS showed both starting material and product. Additional N-bromosuccinimide (6.732 g, 37.82 mmol) was added and the mixture was stirred at rt again. After stirring overnight, the mixture was diluted with water and sodium bicarbonate solution and then the mixture was extracted with EtOAc. The organic layer was washed with water and brine. The EtOAc layer was dried and evaporated in vacuum to a residue, which was purified by chromatography to afford (5-bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)(4-chlorophenyl)methanone as a white solid (18.0, 73.5%). LCMS: (FA) ES+ 451.9, 453.9

[00432] **Step 6:** (5-Bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)(4-chlorophenyl)methanol

[00433] To a solution of {5-bromo-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}(4-chlorophenyl)methanone (11.81 g, 26.08 mmol) in tetrahydrofuran (300 mL, 4000 mmol) was added lithium tetrahydroborate (52.17 mmol, 52.17 mmol) in tetrahydrofuran (26 mL, 320 mmol) under argon. The mixture was stirred at rt for 3h and then cooled down in dry ice-acetone bath. Acetic acid (7.1 mL, 120 mmol) was added. The mixture was stirred for 5 min and saturated aqueous sodium bicarbonate solution was added, followed by EtOAc. The organic layer was separated and washed with brine, then dried over sodium sulfate. The solvent was removed and the residue was purified by column chromatography to afford (5-bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)(4-chlorophenyl)methanol as a white powder (11.2, 94.2%). LCMS: (FA) ES+ 454.0, 456.0

[00434] **Step 7:** (4-chlorophenyl)(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)methanol

[00435] To a mixture of {5-bromo-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}(4-chlorophenyl)methanol (5.19 g, 11.4 mmol) in tetrahydrofuran (146.9 mL, 1811 mmol) was added isopropylmagnesium chloride (1M in THF, 34.2 mL, 34.2 mmol) at -40°C under argon. After addition, the reaction temperature was raised to rt for 15 min. The mixture was then cooled to -78°C and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8.149 mL, 39.94 mmol) was added. After the addition, the mixture was brought to rt. After 1h, the mixture was heated at 75°C overnight. The mixture was cooled to rt and quenched with saturated ammonium chloride solution. The mixture was stirred for 10min then extracted with EtOAc. The organic layer was dried and evaporated in vacuum. The mixture was purified by chromatography to afford (4-chlorophenyl)(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)methanol as a thick oil (5.32g, 65.0%). LCMS: (FA) ES+ 502.2, 504.1.

[00436] **Step 8:** Potassium (4-((4-chlorophenyl)(hydroxy)methyl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-2-yl)trifluoroborate

[00437] To a suspension of (4-chlorophenyl)(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)methanol in methanol (3.5 mL, 87 mmol) under argon was added potassium hydrogen fluoride (3.13 g, 40.0 mmol) in one portion at 0 °C. Water (8.06 mL, 447 mmol) was added dropwise. After the addition, the ice-water bath was removed and the mixture was stirred at rt over the weekend. The mixture was evaporated and the residue was dried under high vaccum. The crude mixture was extracted with hot actone 3 times. The extracts were combined and evaporated to dryness to afford potassium (4-((4-chlorophenyl)(hydroxy)methyl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-2-yl)trifluoroborate as a white powder (6.34g, 100%). LCMS: (AA) ES- 442.2, 444.2, ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.71 (d, J = 2.81 Hz, 1H), 7.35-7.24 (m, 2H), 7.45 (td, J = 4.77, 2.42, 2.42 Hz, 2H), 6.69-6.59 (m, 1H), 6.80 (d, J = 4.16 Hz, 1H), 5.81 (dd, J = 4.74, 1.41 Hz, 1H), 5.57 (td, J = 9.49, 2.15, 2.15 Hz, 1H), 4.02-3.89 (m, 1H), 3.74-3.59 (m, 1H), 2.21-1.88 (m, 3H), 1.76-1.47 (m, 3H).

[00438] **Step 9:** 4-(4-((4-Chlorophenyl)(hydroxy)methyl)-5-(4H-1,2,4-triazol-3-yl)thiophen-2-yl)picolinonitrile (Compound **81**)

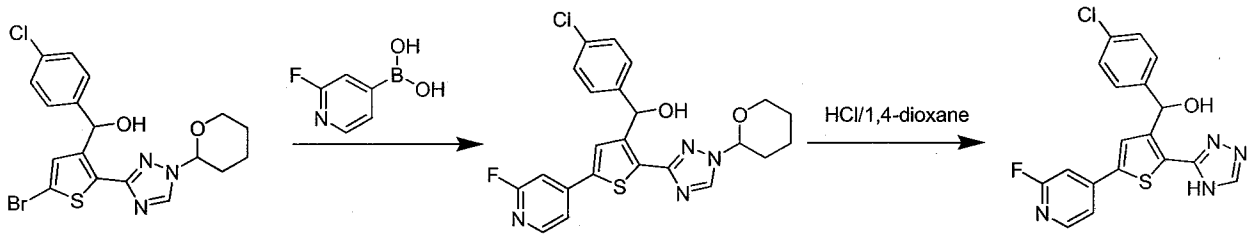
[00439] A mixture of potassium (4-((4-chlorophenyl)(hydroxy)methyl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-2-yl)trifluoroborate (0.133 g, 0.276 mmol), 4-bromo-pyridine-2-carbonitrile (60.6 mg, 0.331 mmol) , 2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl (24.8 mg, 0.0533 mmol), palladium acetate (4.6 mg, 0.020 mmol) and sodium carbonate (77 mg, 0.73 mmol) in ethanol (6.2 mL, 110 mmol) was degassed with argon and then heated at 85°C for 13h. The mixture was absorbed on silica gel and purified by chromatography to afford an intermediate. LCMS: (AA) ES+ 478.1, 480.0. This intermediate in 1,4-dioxane (2.0 mL, 26 mmol), tert-butyl alcohol (2.0 mL, 21 mmol)

and 4.00 M HCl in dioxane(3.0 mL, 14 mmol) was heated at 60°C for 1h. The mixture was evaporated to dryness and then purified by HPLC to afford 4-(4-((4-chlorophenyl)(hydroxy)methyl)-5-(4H-1,2,4-triazol-3-yl)thiophen-2-yl)picolinonitrile (12.4mg, 11.4%). LCMS: (FA) ES+ 394.3, 396.1. 1H NMR (400 MHz, d_6-DMSO) δ: 14.69-13.48 (br, 1H), 8.69 (d, J = 6.79 Hz, 2H), 8.45 (s, 1H), 8.08-7.88 (m, 2H), 7.56 (d, J = 8.39 Hz, 2H), 7.35 (d, J = 8.40 Hz, 2H), 6.79 (s, 1H).

[00440] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 2:

3	LCMS: (AA) ES+ 394, 396.
8	LCMS: (FA) ES+ 399, 401.
10	LCMS: (AA) ES+ 408, 410.
13	LCMS: (AA) ES+ 425, 427.
16	LCMS: (AA) ES+ 387, 389.
17	LCMS: (AA) ES+ 399, 401.
23	LCMS: (FA) ES+ 385, 387.
25	LCMS: (AA) ES+ 403, 405, 407.
42	LCMS: (AA) ES+ 419, 421.
48	LCMS: (AA) ES+ 394, 396.
57	LCMS: (AA) ES+ 425, 427.
64	LCMS: (AA) ES+ 438, 440.
68	LCMS: (FA) ES+ 388, 390.
147	LCMS: (AA) ES+ 451, 453
197	LCMS: (AA) ES- 431, 433, 435

[00441] Example 3: Synthesis of (4-chlorophenyl)[5-(2-fluoropyridin-4-yl)-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (Compound 21)



[00442] **Step 1:** (4-Chlorophenyl){5-(2-fluoropyridin-4-yl)-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}methanol

A mixture of {5-bromo-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}(4-chlorophenyl)methanol (734 mg, 1.61 mmol), 2-fluoro-4-pyridinylboronicacid (455 mg, 3.23 mmol) , tetrakis(triphenylphosphine)palladium(0) (93.3 mg, 0.0807 mmol) and cesium carbonate (1.58 g, 4.84 mmol) in 1,4-dioxane (10.1 mL, 129 mmol) and water (1.45 mL, 80.7 mmol) was irradiated in a microwave oven at 140 °C under argon for 20 min. The reaction mixture was dry loaded onto silica gel and purified by column chromatography (SiO_2, elution with EtOAc in hexanes, 0-80% gradient) to afford (4-chlorophenyl){5-(2-fluoropyridin-4-yl)-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}methanol as a white solid (0.71g, 92.8%). LCMS: (AA) ES+ 471.1, 473.1

[00443] **Step 2:** (4-chlorophenyl)[5-(2-fluoropyridin-4-yl)-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (Compound **21**)

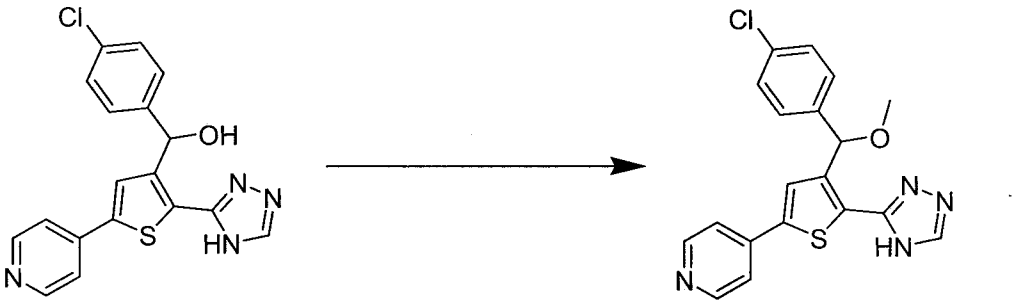
[00444] A mixture of (4-Chlorophenyl){5-(2-fluoropyridin-4-yl)-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}methanol (0.261 g, 0.554 mmol), tert-butyl alcohol (3.9 mL, 41 mmol), 1,4-dioxane (2.6 mL, 33 mmol) and 4.00 M HCl in dioxane(3.66 mL, 16.6 mmol) was heated at 70 °C for 2 h. The mixture was cooled down. A small amount of water was added, followed by the addition of sodium bicarbonate (0.745 g, 8.87 mmol). The mixture was stirred for 10 min and then evaporated in vacuum. The residue was purified by (HPLC to afford 4-chlorophenyl)[5-(2-fluoropyridin-4-yl)-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol as a white solid. LCMS: (AA) ES+ 387.2, 389.1; 1H NMR (300 MHz, d_4-methanol) δ: 8.51 (s, 1H), 8.18 (d, J = 5.41 Hz, 1H), 7.73 (s, 1H), 7.60-7.44 (m, 3H), 7.37-7.23 (m, 3H), 6.76 (s, 1H).

[00445] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 3:

11	LCMS: (AA) ES+ 383, 385.
14	LCMS: (AA) ES+ 403, 405, 407.
26	LCMS: (AA) ES+ 387, 389.

30	LCMS: (AA) ES+ 403, 405, 407.
34	LCMS: (AA) ES+ 387, 389.
40	LCMS: (AA) ES+ 403, 405, 407.
41	LCMS: (AA) ES+ 426, 428.
43	LCMS: (AA) ES+ 383, 385.
45	LCMS: (AA) ES+ 387, 389.
52	LCMS: (AA) ES+ 369, 371.
55	LCMS: (AA) ES+ 370, 372.
59	LCMS: (AA) ES+ 370, 372.
69	LCMS: (AA) ES+ 383, 385.
75	LCMS: (AA) ES+ 384, 386.
77	LCMS: (AA) ES+ 369, 371.
79	LCMS: (AA) ES+ 370, 372.
84	LCMS: (AA) ES+ 369, 371.

[00446] Example 4: Synthesis of 4-[4-[(4-chlorophenyl)(methoxy)methyl]-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (Compound 6)



[00447] To a solution of (4-chlorophenyl)[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (100 mg, 0.271 mmol) in methanol (10 mL) was added conc. HCl (2.0 mL, 24 mmol) and the mixture was stirred at rt overnight. The reaction mixture was concentrated and basified by sodium bicarbonate, loaded on silica gel and purified by column chromatography (SiO2, elution with 0-5% MeOH in DCM) to afford the title compound (80 mg, 78%). LCMS: (AA) ES+ 383.3, 385.2; 1H NMR (300 MHz, , d_6-

DMSO) δ: 8.70 (s, 1H), 8.57 (d, J = 4.80 Hz, 2H), 7.79 (s, 1H), 7.68 (d, J = 4.79 Hz, 2H), 7.56 (d, J = 8.25 Hz, 2H), 7.38 (d, J = 8.30 Hz, 2H), 6.50 (s, 1H), 3.31 (d, J = 9.06 Hz, 3H).

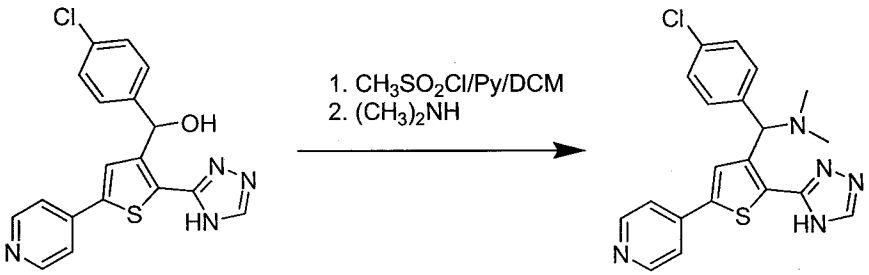
[00448] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 4:

220	LCMS: (AA) ES+ 440, 442.

[00449]

[00450] Example 5: Synthesis of 1-(4-chlorophenyl)-N,N-dimethyl-1-[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3- yl)-3-thienyl]methanamine (Compound 9)

[00451]



[00452] To a mixture of (4-chlorophenyl)[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (141 mg, 0.382 mmol) (synthesized in an analogous way as described in Example 3) in methylene chloride (2.8 mL) was added pyridine (6.0 mL, 74 mmol) and methanesulfonyl chloride (0.148 mL, 1.91 mmol) at 0°C. After the addition, the mixture was warmed to rt and stirred for 30min and then heated at 60°C for 20min. The mixture was cooled in an ice bath and dimethylamine (0.553 mL, 11.5 mmol) in THF was added to the mixture. After the addition, the ice bath was removed and the mixture was stirred at rt for 30min and then heated at 55°C for 2h. The mixture was cooled, concentrated, and the residue was purified by HPLC to afford 1-(4-chlorophenyl)-N,N-dimethyl-1-[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanamine as white powder (115mg, 76%). LCMS: (AA) ES+ 396.3, 398.1; ^{1}H NMR (400 MHz, d_6-DMSO) δ: 14.48-14.27 (m, 1H), 8.71 (s, 1H), 8.57 (dd, J = 4.55, 1.62 Hz, 2H), 7.95 (s, 1H), 7.73-7.63 (m, 4H), 7.39-7.30 (m, 2H), 5.53 (s, 1H), 2.13 (s, 6H).

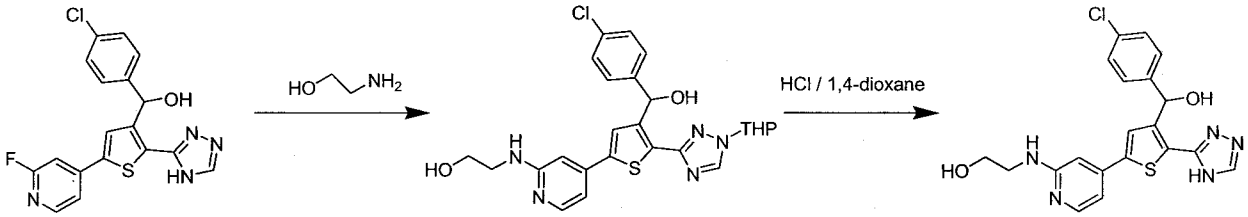
[00453] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 5:

33	LCMS: (AA) ES+ 410, 412.
44	LCMS: (AA) ES+ 396, 398.
51	LCMS: (AA) ES+ 408, 410.
65	LCMS: (AA) ES+ 396, 398.

86	LCMS: (AA) ES+ 453, 455.
90	LCMS: (AA) ES+ 465, 467
135	LCMS: (AA) ES+ 507, 509.
139	LCMS: (AA) ES+ 508, 510
146	LCMS: (FA) ES+ 520, 522
151	LCMS: (AA) ES+ 465, 467
152	LCMS: (FA) ES+ 510, 512
154	LCMS: (FA) ES+ 494, 496
161	LCMS: (AA) ES+ 410, 412
163	LCMS: (AA) ES+ 508, 510
164	LCMS: (AA) ES+ 495, 497.
167	LCMS: (AA) ES+ 476, 478
173	LCMS: (AA) ES+ 508, 510
176	LCMS: (AA) ES+ 465, 467
182	LCMS: (AA) ES+ 495, 497
183	LCMS: (AA) ES+ 496, 498.
185	LCMS: (AA) ES+ 411, 413
192	LCMS: (AA) ES+ 509, 511.
196	LCMS: (AA) ES+ 536, 538
200	LCMS: (AA) ES+ 480, 482
201	LCMS: (AA) ES+ 481, 483
204	LCMS: (AA) ES+ 453, 455
206	LCMS: (AA) ES+ 476, 478
208	LCMS: (AA) ES+ 508, 510
209	LCMS: (AA) ES+ 508, 510

212	LCMS: (AA) ES+ 495, 497.
216	LCMS: (AA) ES+ 501, 503
221	LCMS: (AA) ES+ 529, 531
224	LC/MS: (FA) ES+ 572, 574; ES- 570, 572.
229	LCMS: (AA) ES+ 495, 497.
234	LCMS: (AA) ES+ 508, 510
240	LCMS: (AA) ES+ 507, 509
241	LCMS: (AA) ES+ 465, 467
242	LCMS: (AA) ES+ 507, 509
243	LCMS: (AA) ES+ 458, 460
247	LCMS: (AA) ES+ 507, 509
248	LCMS: (AA) ES+ 495, 497
251	LCMS: (AA) ES+ 442, 444
254	LCMS: (FA) ES+ 452, 454
259	LCMS: (AA) ES+ 509, 511.
261	LCMS: (AA) ES+ 453, 455
267	LCMS: (AA) ES+ 508, 510
268	LCMS: (AA) ES+ 509, 511.
270	LCMS: (AA) ES+ 508, 510
283	LCMS: (AA) ES+ 509, 511.

[00454] Example 6: Synthesis of 2-({4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(4H-1,2,4-triazol-3-yl)-2- thienyl]pyridin-2-yl}amino)ethanol (Compound 49)

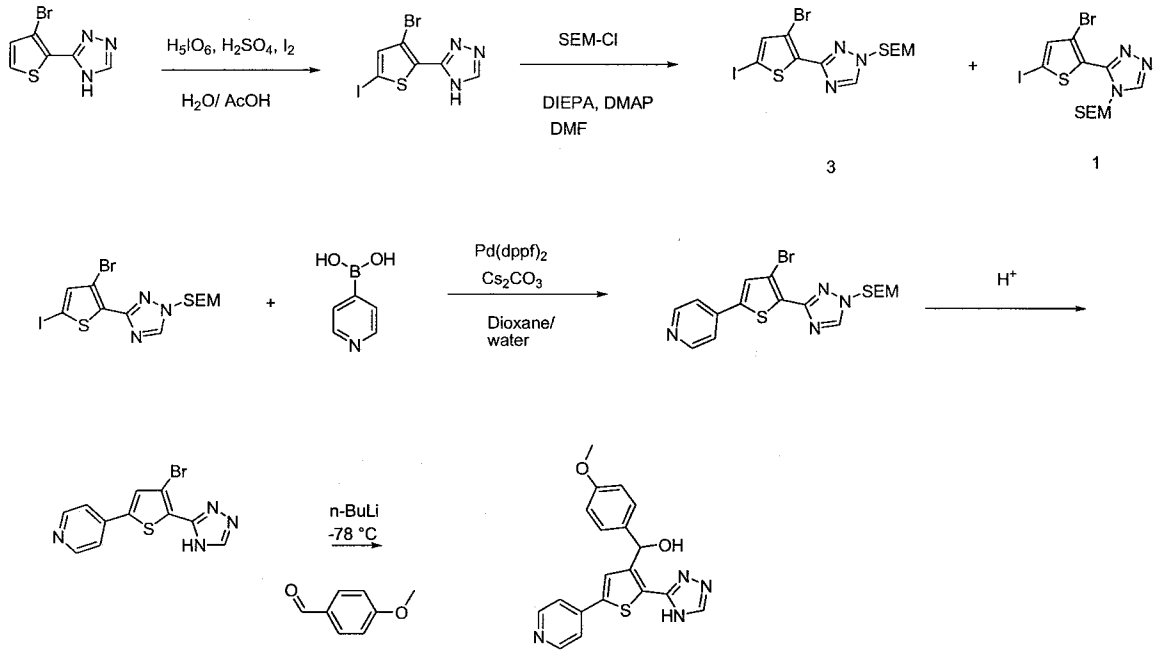


[00455] A mixture of (4-chlorophenyl){5-(2-fluoropyridin-4-yl)-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}methanol (80.0 mg, 0.170 mmol), ethanolamine (0.104 g, 1.70 mmol) and N,N-diisopropylethylamine (0.118 mL, 0.679 mmol) in dimethylsulfoxide (0.5 mL, 7 mmol) was heated at 200°C for 1h under argon. The reaction mixture was cooled, diluted with water and extracted with butanol. The butanol layer was collected and evaporated to a residue which was purified by chromatography (SiO_2, elution with 0-20 % MeOH in DCM) to afford the intermediate. The intermediate in 1,4-dioxane (1.0 mL, 13 mmol) and conc HCl (1.0 mL, 12 mmol) was stirrred at rt for 1h. The solvent was evaporated and the residue was purified by chromatography (SiO_2, elution with 0-70% (MeOH/DCM/NH4OH, 13/85/2) in DCM) to afford 2-({4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}amino)ethanol (17.6mg, 24.2%). LCMS: (AA) ES+ 428.2, 430.0; ^{1}H NMR (400 MHz, d_6-DMSO) δ: 14.66-14.13 (m, 1H), 8.68 (s, 1H), 7.94 (d, J = 5.30 Hz, 1H), 7.58-7.48 (m, 3H), 7.38-7.30 (m, 2H), 6.81-6.68 (m, 3H), 6.60 (s, 1H), 4.72 (s, 1H), 3.57-3.45 (m, 2H), 3.34 (d, J = 5.88 Hz, 3H).

[00456] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 6:

28	LCMS: (AA) ES+ 435, 437.
62	LCMS: (AA) ES+ 398, 400.

[00457] Example 7: Synthesis of (4-methoxyphenyl)[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (Compound 85)



[00458] **Step 1:** 3-(3-Bromo-5-iodo-2-thienyl)-4H-1,2,4-triazole.

To a mixture of 3-(3-bromo-2-thienyl)-4H-1,2,4-triazole (1.12 g, 4.87 mmol), iodine (1.12 g, 4.41 mmol) and periodic acid (4.80 g, 24.8 mmol) in acetic acid (11.0 mL, 200 mmol) were added water (8.0 mL, 400 mmol) and sulfuric acid (2.0 mL, 40 mmol) and the reaction mixture was stirred at rt for two days. The resulting white precipitate was collected by filtration. The solid cake was washed with water and dried under high vacuum at 40°C to yield product as a white solid (1.74 g, 100% yield, as a white solid). LCMS: (FA) ES^+, 357.7. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.63(s, 1H), 7.43 (s, 1H)

[00459] **Step 2**: 3-(3-Bromo-5-iodo-2-thienyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole.

[00460] Into a solution of 3-(3-bromo-5-iodo-2-thienyl)-4H-1,2,4-triazole (500.0 mg, 1.40 mmol), N,N-dimethylaminopyridine (17.2 mg, 0.140 mmol) and N,N-diisopropylethylamine (0.32 mL, 1.83 mmol) in N,N-dimethylformamide (17.0 mL, 220 mmol) was added [β-(Trimethylsilyl)ethoxy]methyl chloride (0.270 mL, 1.55 mmol) was added and the solution was stirred for 2 h at rt. Water(5.0 mL) and EtOAc (5mL) were added , the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, concentrated and the obtained residue was purified by column chromatography (SiO_2, elution with 0-30% EtOAc in hexane) to give the title compound as a yellowish oil (653 mg, (87% major isomer, 13% minor isomer) LCMS: (FA) ES^+, 486, 488. (major isomer)^1H NMR (400 MHz, d_6-DMSO) δ: 8.81(s, ,1H), 7.45 (s, 1H), 5.540-5.545 (s, br, 2H), 3.62-3.66 (m, 2H), 0.840-0.880(m, 2H), -0.05 (s, 9H). LCMS: (FA) ES^+, 486, 488. (minor isomer)^1H NMR (400 MHz, d_6-DMSO) δ: 8.215(s, ,1H), 7.615 (s, 1H), 5.48(s, br, 2H), 3.44-3.50 (m, 2H), 0.75-0.80(m, 2H), -0.08 (s, 9H).

[00461] **Step 3:** 4-[4-Bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridine.

[00462] A mixture of 3-(3-bromo-5-iodo-2-thienyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole (653.0 mg, 1.34 mmol), pyridine-4-boronic acid (248 mg, 2.02 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloride (55.2 mg, 0.067 mmol) and cesium carbonate (1.80 g, 5.37 mmol) in 1,4-dioxane (8.40 mL, 107 mmol) and water (1.2mL, 67.1 mmol) was heated at 110°C under an atmosphere of argon overnight. Water(3mL) and EtOAc (3mL) were added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, concentrated and the obtained residue was purified by column chromatography (SiO_2, elution with 0-10 % MeOH in DCM) to give the title compound as a white solid (438 mg, 74.6 %). LCMS: (FA) ES^+, 438, 440. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.87(s, 1H), 8.62-8.64 (dd, J = 1.5 Hz, 2H), 7.98 (s, 1H), 7.30-7.75 (dd, J = 1.5, 2H), 5.58-5.59 (s, br, 2H), 3.40-3.69 (m, 2H), 0.840-0.890(m, 2H), -0.04 (s, 9H).

[00463] **Step 4:** 4-[4-Bromo-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridine.

[00464] 4-[4-Bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (111.0 mg, 0.224 mmol) was dissolved in methylene chloride (3.0 mL, 47 mmol). Trifluoroacetic acid (3.0 mL, 39 mmol) was added and the solution was stirred at rt overnight. After the reaction was completed saturated $NaHCO_3$ (1mL) was added and the reaction was stirred at rt for 20 min. EtOAc (5mL) was added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, concentrated and the obtained residue was purified by column chromatography (SiO_2, elution with 2-20 % MeOH in DCM) to give the title compound as a yellow solid (222 mg, 54 %). LCMS: (FA) ES^+, 307, 309. ^1H NMR (400 MHz, d_6-DMSO)) δ: 14.5(s,br,1H), 8.70-8.72 (dd, J = 1.5 Hz, 2H), 8.10 (s, 1H), 7.90-7.94 (dd, J = 1.5 Hz, 2H)

[00465] **Step 5**: (4-Methoxyphenyl)[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (Compound **85**)

[00466] To a mixture of 4-[4-bromo-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (222.0 mg, 0.730 mmol) in tetrahydrofuran (5.9 mL, 72.3 mmol) cooled to -78°C was added dropwise n-BuLi in hexanes(2.50 M, 1.2 mL, 2.90 mmol) under an atmosphere of argon and and the mixture was stirred at -78°C for 30 min. To the solution was added dropwise a solution of 4-methoxybenzaldehyde (0.53 mL, 4.34 mmol) in tetrahydrofuran (5.0 mL, 60 mmol) and the resulting solution was stirred for 30 min at -78°C. The reaction mixture was quenched by the addition of water (2mL) and the resulting mixture was warmed to room temperature and stirred for 30 min. The mixture was extracted with EtOAc (5mL) then the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under the reduced pressure. The obtained residue was purified by prep HPLC to yield 62.0 mg as a yellow solid (23.5%). LCMS: (FA) ES^+, 365. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.68(s, 1H), 8.55-8.57 (dd, J = 1.5

Hz , 2H), 7.81(s, br, 1H), 7.63-7.65(dd, J = 1.5 Hz , 2H), 7.40-7.44(d, , J = 8.78 Hz, 2H), 6.82-6.84(d, J = 8.78 Hz, 2H), 6.72 (s, br, 1H), 3.68-3.69 (s, br, 3H).

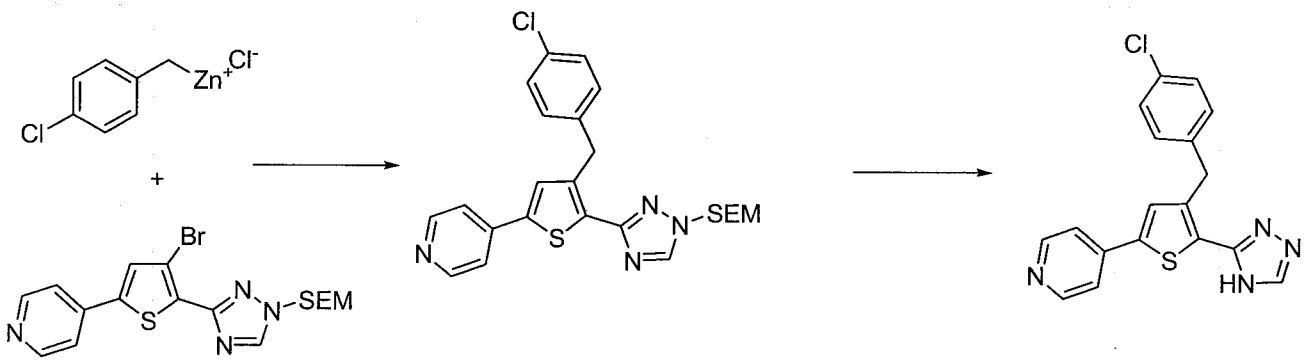
[00467] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 7:

130	LCMS: (FA) ES+ 383.4
132	LCMS: (FA) ES+ 386.3
133	LCMS: (FA) ES+ 418.3
134	LCMS: (FA) ES+ 415.3
136	LCMS: (FA) ES+ 403
138	LCMS: (FA) ES+ 367.4
141	LCMS: (FA) ES+ 363.3
142	LCMS: (FA) ES+ 403.3
155	LCMS: (FA) ES+ 353.4
158	LCMS: (FA) ES+ 379.4
159	LCMS: (FA) ES+ 403.3
162	LCMS: (FA) ES+ 371.3
169	LCMS: (FA) ES+ 387.3
171	LCMS: (FA) ES+ 386.4
174	LCMS: (FA) ES+ 363.5
175	LCMS: (FA) ES+ 386.4
183	LCMS: (FA) ES+ 381.4
186	LCMS: (FA) ES+ 417, 419.
187	LCMS: (FA) ES+ 387.3
188	LCMS: (FA) ES+ 367.4
191	LCMS: (FA) ES+ 399.4
193	LCMS: (FA) ES+ 403.4

198	LCMS: (FA) ES+ 411.
199	LCMS: (FA) ES+ 371.4
202	LCMS: (FA) ES+ 379.4
203	LCMS: (FA) ES+ 403.
207	LCMS: (FA) ES+ 412.3
208	LCMS: (FA) ES+ 385.
214	LCMS: (FA) ES+ 412.4
215	LCMS: (FA) ES+ 393.
217	LCMS: (FA) ES+ 369.4
219	LCMS: (FA) ES+ 403.4
228	LCMS: (FA) ES+ 385.4
231	LCMS: (FA) ES+ 413.3
232	LCMS: (FA) ES+ 387.3
233	LCMS: (FA) ES+ 419.2
235	LCMS: (FA) ES+ 371.3
236	LCMS: (FA) ES+ 413.4
239	LCMS: (FA) ES+ 383.4
246	LCMS: (FA) ES+ 395.4
249	LCMS: (FA) ES+ 365.3
252	LCMS: (FA) ES+ 413.4
253	LCMS: (FA) ES+ 363.3
256	LCMS: (FA) ES+ 379.4
257	LCMS: (FA) ES+ 386.4
258	LCMS: (FA) ES+ 412.3
260	LCMS: (FA) ES+ 403.2

263	LCMS: (FA) ES+ 387.3
264	LCMS: (FA) ES+ 383.4
266	LCMS: (FA) ES+ 371.3
271	LCMS: (FA) ES+ 355.4
272	LCMS: (FA) ES+ 366.3
275	LCMS: (FA) ES+ 387.4
276	LCMS: (FA) ES+ 412.3
279	LCMS: (FA) ES+ 417, 419.
280	LCMS: (FA) ES+ 385.
281	LCMS: (FA) ES+ 403.
284	LCMS: (FA) ES+ 403

[00468] Example 8: Synthesis of 4-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (Compound 5)



[00469] Step 1: 4-[4-(4-Chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4- triazol-3-yl)-2-thienyl]pyridine

[00470] Bis(tri-*t*-butylphosphine)palladium(0) (4.38 mg, 0.00857 mmol) and 4-[4-bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (0.075 g, 0.17 mmol) were combined in a dry round bottomed flask fitted with a stirbar and sealed with a septum. The flask was evacuated/refilled with nitrogen three times then a solution of 4-chlorobenzylzinc chloride in tetrahydrofuran (0.50M, 0.720 mL, 0.360 mmol) was added dropwise via a syringe. A nitrogen line was

attached and the reaction was stirred at rt for 30 minutes, then at 60°C for ~2 hours. The reaction was cooled to rt, diluted with EtOAc and saturated ammonium chloride solution, then the mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted twice more with EtOAc. The organics were combined, washed with bicarbonate solution, then brine, then dried over sodium sulfate. The mixture was filtered then evaporated in vacuo and the residue was purified by column chromatography on silica, elution 100% hexane to 100% EtOAc to afford the title compound as a light yellow oil. Yield 63 mg (76% yield). LCMS: (FA) ES+, 483, 485.

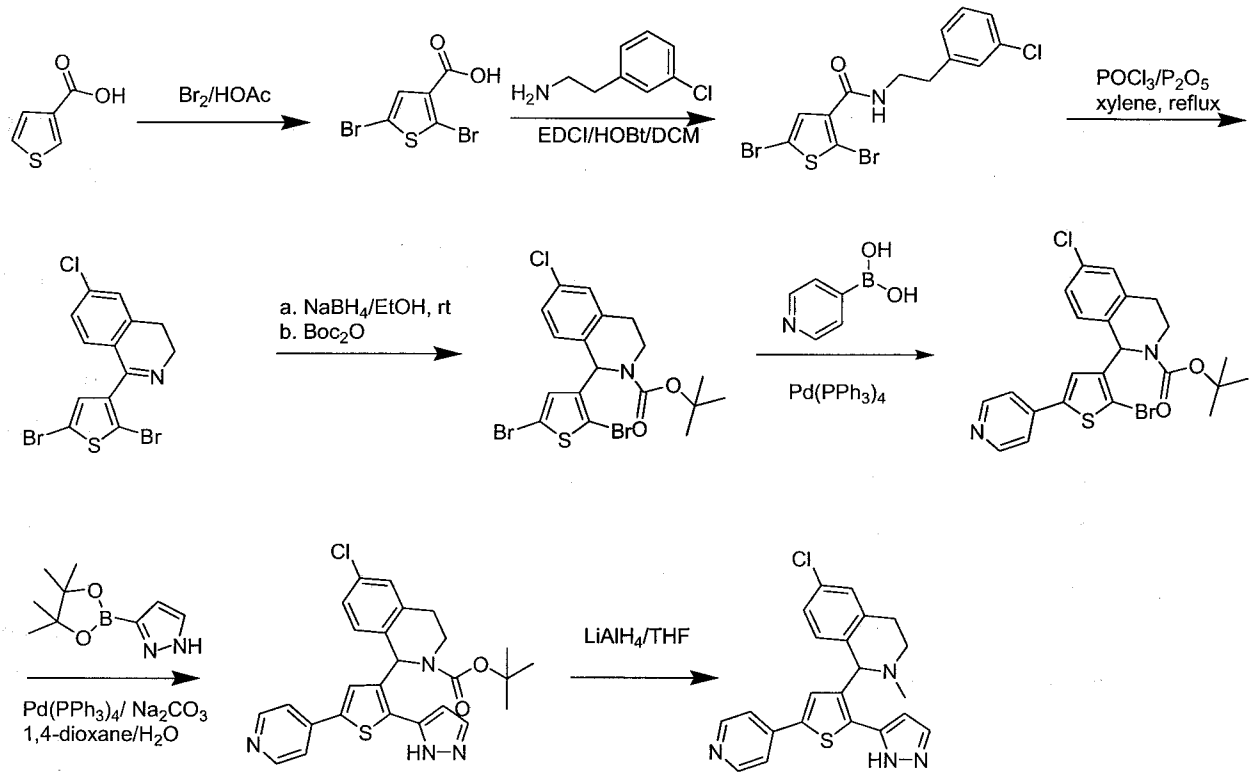
[00471] **Step 2:** 4-[4-(4-Chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (Compound **5**)

[00472] The 4-[4-(4-chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (58 mg, 0.12 mmol) and methylene chloride (4.0 mL, 62 mmol) were combined in a round bottomed flask equipped with a stirbar. The mixture was stirred and trifluoroacetic acid (1.1 mL, 14 mmol) was added in one portion. The resulting yellow solution was stirred overnight at rt under an atmosphere of nitrogen. Excess solvent was removed on the rotovap and the residue was digested in a mixture of EtOAc and aqueous sodium bicarbonate solution. The mixture was stirred then transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted twice more with EtOAc. The organics were combined, washed with bicarbonate solution, then saline, and then dried over sodium sulfate. The mixture was filtered then evaporated in vacuo and the residue was purified by column chromatography on silica, elution 100% DCM to 100% EtOAc to afford the title compound as an off-white powder. Yield 41 mg (97% yield). LCMS: (FA) ES+, 353, 355. ^{1}H NMR (400MHz, d_6-DMSO) δ: 14.31 (1H, br s), 8.67 (1H, br s), 8.55 (2H, d, J = 6.3 Hz), 7.69 (1H, s), 7.63 (2H, d, J = 6.3 Hz), 7.36-7.30 (4H, m), 4.47 (2H, s).

[00473] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 8:

87	LCMS: (FA) ES+ 370.

[00474] **Example 9: Synthesis of 6-chloro-2-methyl-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-1,2, 3,4-tetrahydroisoquinoline (Compound 58)**



[00475] **Step 1:** 2,5-Dibromo-3-thenoic Acid

[00476] In a 500 mL round bottomed flask was placed 3-thenoic acid (16.04 g, 125.2 mmol) and acetic acid (200 mL, 4000 mmol). To the mixture was added bromine (32.24 mL, 625.8 mmol) and the mixture was stirred for 18 h at 60 °C. The mixture was allowed to cool to rt then was diluted with ice-water. Sodium bisulfite (52.10 g, 500.7 mmol) was added. The resulting precipitate was collected by filtration and then washed with water to give 5-dibromo-3-thenoic acid as an off-white powder (33.4, 93.3%). LCMS (FA) ES+ 284.9, 286.9.

[00477] **Step 2:** 2,5-dibromo-N-[2-(3-chlorophenyl)ethyl]thiophene-3-carboxamide

[00478] To a mixture of 2,5-dibromo-3-thenoic Acid (10.0 g, 35.0 mmol), 2-(3-chlorophenyl)ethanamine (7.08 g, 45.5 mmol) and 1-hydroxybenzotriazole hydrate (5.89 g, 38.5 mmol) in methylene chloride (291 mL, 4550 mmol) was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (12.1 g, 62.9 mmol). The mixture was stirred at rt overnight. The reaction mixture was washed with 1NHCl, water, saturated sodium bicarbonate and brine. The DCM layer was dried and evaporated to afford 5-dibromo-N-[2-(3-chlorophenyl)ethyl]thiophene-3-carboxamide (14.7, 99.2%). LCMS (FA) ES+ 423.9, 425.9.

[00479] **Step 3:** 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline

[00480] To a mixture of 2,5-dibromo-N-[2-(3-chlorophenyl)ethyl]thiophene-3-carboxamide (5.15 g, 12.2 mmol) in xylenes (25.98 mL, 70.32 mmol) at 70°C was added phosphorus pentoxide (13.0 g, 45.8

mmol) and then phosphoryl chloride (12.0 mL, 129 mmol). The mixture was heated at 150°C for 60h, then the mixture was cooled to rt. The solution was removed by decantation and washed with toluene twice. Water (20mL) and 20% NaOH (20mL) were added and the mixture was sonicated. The mixture was extracted with EtOAc. The organic layer was washed with water, dried over MgSO4, and evaporated in vacuo to give a residue which was purified by chromatography to afford 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline as foam solid (2.8g, 57%).

[00481] **Step 4:** tert-Butyl 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

[00482] To a mixture of 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline (2.60 g, 6.41 mmol) in ethanol (37.43 mL, 641.1 mmol) was added di-tert-butyldicarbonate (2.80 g, 12.8 mmol) and sodium tetrahydroborate (0.485 g, 12.8 mmol) at 0°C. The mixture was stirred for 20min at 0°C and then overnight at rt. The reaction mixture was concentrated and the residue was extracted with EtOAc. The organic layer was separated, washed with water, washed with brine, and then dried over MgSO4. The solvent was evaporated and the residue was purified by chromatography to afford tert-butyl 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline-2(1H)- carboxylate as a white powder (2.45g, 75.3%).

[00483] **Step 5:** tert-Butyl 1-(2-bromo-5-pyridin-4-yl-3-thienyl)-6-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate

[00484] A mixture of tert-butyl 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (177.0 mg, 0.3486 mmol), pyridine-4-boronic acid (51.43 mg, 0.4184 mmol) tetrakis(triphenylphosphine)palladium(0) (20.1 mg, 0.0174 mmol) and cesium carbonate (0.341 g, 1.04 mmol) in 1,4-dioxane (6.0 mL, 77 mmol) and water (2.0 mL, 110 mmol) was degassed and heated at 100 °C for 1h. The mixture was extracted with EtOAc. The organic layer was separated and washed with water. The organic layer was dried and evaporated to leave a residue which was purified by chromatography to afford tert-butyl 1-(2-bromo-5-pyridin-4-yl-3-thienyl)-6-chloro-3,4-dihydroisoquinoline- 2(1H)-carboxylate as a white solid (72mg, 41%). LCMS AA ES+ 505.1, 507.1

[00485] **Step 6:** tert-Butyl 6-chloro-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-3, 4-dihydroisoquinoline-2(1H)-carboxylate

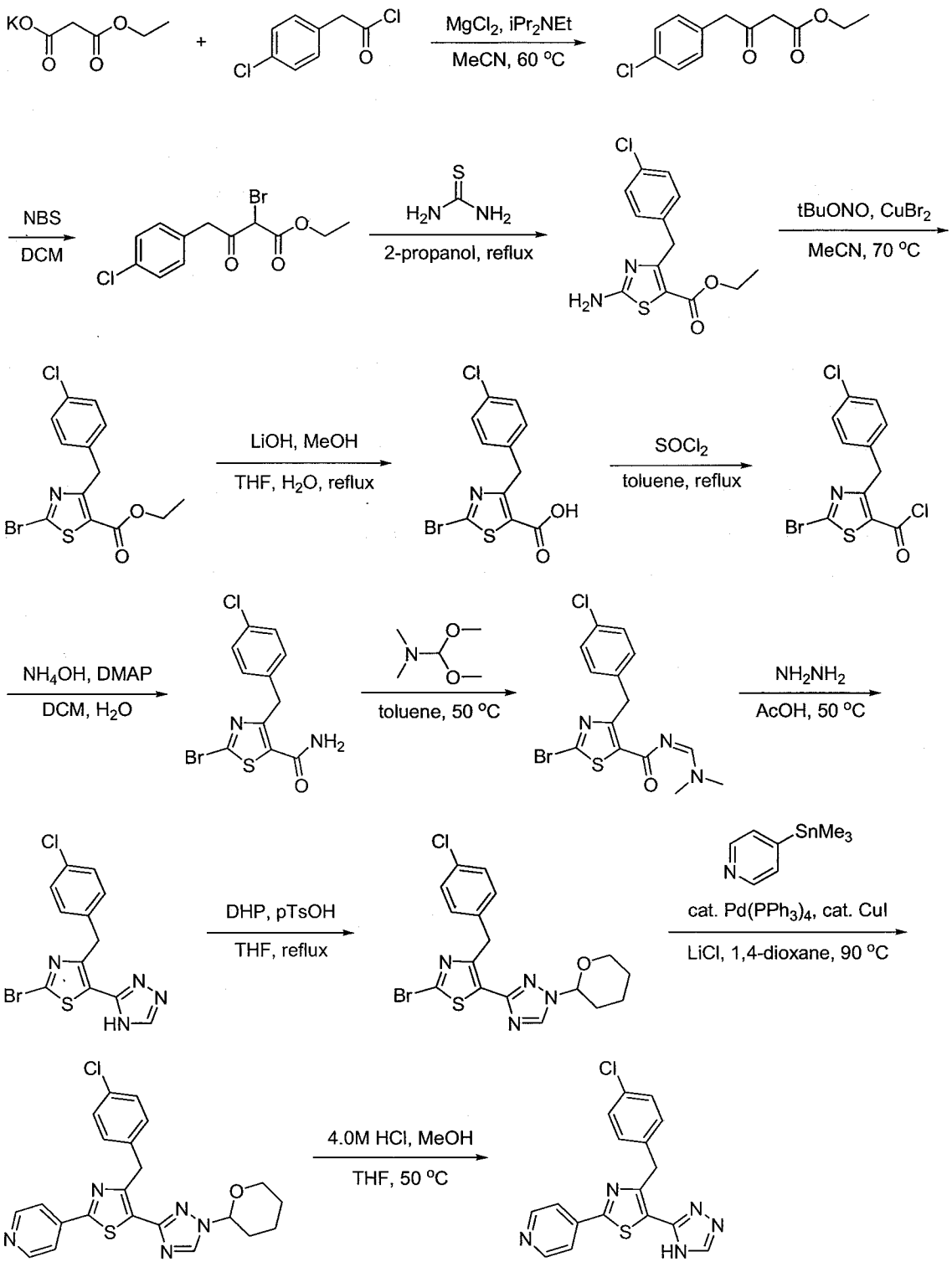
[00486] A mixture of tert-butyl 1-(2-bromo-5-pyridin-4-yl-3-thienyl)-6-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate (72.0 mg, 0.142 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxabolone)-pyrrazole (27.6 mg, 0.142 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloride (11.7 mg, 0.0142 mmol) and sodium carbonate (29 mg, 0.27 mmol) in 1,2-dimethoxyethane (3.0 mL, 29 mmol) and water (1.0 mL, 56 mmol) was heated at 95°C for 4.5h. A LCMS showed the desired product together with unreacted starting material. Aditional [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloride (11.7 mg, 0.0142 mmol) 3-

(4,4,5,5-Tetramethyl-1,3,2-dioxabolone)-pyrrazole (56 mg, 0.29 mmol), tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.013 mmol), sodium carbonate (100 mg, 0.9 mmol) and 1,2-dimethoxyethane (3.0 mL, 29 mmol) were added. The mixture was heated at 100°C for another 4h. The mixture was dry-loaded onto silica gel and purified by chromatography to afford tert-butyl 6-chloro-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-3, 4-dihydroisoquinoline-2(1H)-carboxylate (41mg, 58%). LCMS AA ES+ 493.2, 495.1.

[00487] **Step 7:** 6-Chloro-2-methyl-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-1,2, 3,4-tetrahydroisoquinoline (Compound **58**)

[00488] To a solution of tert-butyl 6-chloro-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-3,4-dihydroisoquinoline-2(1H)-carboxylate (41 mg, 0.083 mmol) in tetrahydrofuran (3.0 mL, 37 mmol) was added lithium tetrahydroaluminate (0.249 mmol, 0.249 mmol) in THF (2.0mM) at -78°C. After the addition, the temperature of the reaction was raised to rt for 30 min and then heated at 85°C for 5h. The mixture was quenched with water, diluted with methanol, and extracted with ethyl acetate. The organic phase was dried, filtered and evaporated. The residue was loaded onto silica gel and purified by chromatography to afford 6-chloro-2-methyl-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-1,2, 3,4-tetrahydroisoquinoline (5.1mg, 15%). LCMS AA ES+ 407.2, 409.1; ^{1}H NMR (400 MHz, d_4-methanol) δ: 8.48 (d, J = 5.06 Hz, 2H), 7.89-7.66 (m, 1H), 7.61 (s, 2H), 7.50-7.31 (br, 1H), 7.17 (s, 1H), 7.00 (d, J = 7.98 Hz, 1H), 6.87-6.48 (m, 2H), 5.16-4.94 (m, 1H), 3.34 (s, 1H), 3.28-3.10 (m, 2H), 2.94-2.79 (m, 1H), 2.72-2.56 (m, 1H), 2.26 (s, 3H)

[00489] **Example 10: Synthesis of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound 76)**



[00490] **Step 1:** Ethyl 4-(4-chlorophenyl)-3-oxobutanoate.

[00491] To a suspension of potassium ethyl malonate (17.12 g, 100.6 mmol) in acetonitrile (150 mL) were added N,N-diisopropylethylamine (28 mL, 160 mmol) and magnesium chloride (12.11 g, 127.2

mmol). The resulting mixture was stirred for 1 hour. A solution of 4-chlorophenylacetyl chloride (10.12 g, 53.53 mmol) in acetonitrile (100 mL) was then added and the mixture was heated to 60° C and stirred for 20 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was suspended in 1N aqueous HCl (250 mL) and was extracted with EtOAc (100 mL x 2). The combined organic phases were dried over anhydrous MgSO4 and insoluble materials were removed by filtration. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica, elution with a 0%-80% mixture of EtOAc in hexane (linear gradient, 45 min) to obtain ethyl 4-(4-chlorophenyl)-3-oxobutanoate (5.0 g, 39%) as a yellow oil. LC/MS (FA) ES- 239. ^{1}H NMR (d_6-DMSO, 400 MHz): δ: 7.37 (2H, d, J = 13.8 Hz), 7.20 (2H, d, J = 13.8 Hz), 4.07 (2H, q, J = 7.2 Hz), 3.89 (2H, s), 3.66 (2H, s), 1.17 (3H, t, J = 7.2 Hz).

[00492] **Step 2:** Ethyl 2-bromo-4-(4-chlorophenyl)-3-oxobutanoate

[00493] In a 250 mL round bottomed flask were placed ethyl 4-(4-chlorophenyl)-3-oxobutanoate (4.04 g, 16.8 mmol) and methylene chloride (100 mL). To the solution was added N-bromosuccinimide (3.13 g, 17.6 mmol) and the mixture was stirred for 3 h at rt. To the mixture was added a freshly prepared 10% aqueous solution of NaHSO3 (5 g $NaHSO_3$ dissolved in 50 mL water) and the resulting biphasic mixture was vigorously stirred for 15 min at rt. The organic phase was separated and the aqueous phase was extracted with DCM (30 mL). The organic phases were combined and washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and dried over anhydrous $MgSO_4$. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residual yellow oil was essentially pure and was used in the next step without further purification. LC/MS (FA) ES- 319.

[00494] **Step 3:** Ethyl 2-amino-4-(4-chlorobenzyl)thiazole-5-carboxylate

[00495] In a 100 mL round bottomed flask were placed ethyl 2-bromo-4-(4-chlorophenyl)-3-oxobutanoate (990 mg, 3.1 mmol) and isopropyl alcohol (20 mL). To the mixture was added thiourea (590 mg, 7.8 mmol) and the reaction was then refluxed for 16 h with stirring. The mixture was allowed to cool to rt and was then concentrated under reduced pressure. The residue was suspended in EtOAc (50 mL) and then washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), brine (50 mL), and dried over anhydrous MgSO4. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residual off-white yellowish crystalline solid was essentially pure by LCMS and was used in the next step without further purification. LC/MS (FA) ES+ 296. ^{1}H NMR (d_6-DMSO, 400 MHz): δ: 7.80 (2H, br s), 7.32 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 8.8 Hz), 4.14—4.20 (4H, m), 1.22 (3H, t, J = 7.1 Hz).

[00496] **Step 4:** Ethyl 2-bromo-4-(4-chlorobenzyl)thiazole-5-carboxylate.

In a 250 mL round bottomed flask were placed ethyl 2-amino-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (786 mg, 2.65 mmol) and acetonitrile (75 mL). To the mixture was added copper (II) bromide

(963 mg, 4.31 mmol). The suspension was stirred for 15 min at rt. To the mixture was added tert-butyl nitrite (0.630 mL, 5.30 mmol) and the stirring was continued for an additional 1.5 h at 70° C. The reaction mixture was allowed to cool to rt and was then concentrated under reduced pressure. The residue was purified by column chromatography on silica, elution with a 10%-50% mixture of EtOAc in hexane to obtain ethyl 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (820 mg; 86%) as an yellow syrup, which spontaneously solidified on standing at rt to afford off-white crystalline solid. LC/MS (FA) ES+ 362. ^{1}H NMR (CDCl3, 400 MHz): δ: 7.29 (2H, d, J = 8.8 Hz), 7.24 (2H, d, J = 8.8 Hz), 4.44 (2H, s), 4.35 (2H, q, J = 7.3 Hz), 1.36 (3H, t, J = 7.3 Hz).

[00497] **Step 5:** Ethyl 2-bromo-4-(4-chlorobenzyl)thiazole-5-carboxylic acid.

[00498] In a 100 mL round bottomed flask were placed ethyl 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (955 mg, 2.65 mmol) and tetrahydrofuran (50 mL, 600 mmol). To this solution was added a freshly prepared aqueous solution of lithium hydroxide [(lithium hydroxide•H_2O (177 mg, 4.22 mmol) and water (15 mL, 830 mmol)). The mixture was stirred for 4 h at rt then MeOH (20 mL) was added and the mixture was refluxed for 3 h. The mixture was allowed to cool to rt and then acidified by the addition of 1.0N HCl aq (4.5 mL). The mixture was stirred for 1 h at rt. The mixture was then concentrated under reduced pressure until reduced to ca 5 mL volume. EtOAc (50 mL) was added and the mixture was washed with water (50 mL), then brine (50 mL), then was dried over anhydrous MgSO4. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residual yellow crystalline solid was used in the next step without further purification. LC/MS (FA) ES+ 332.

[00499] **Steps 6 and 7:** 2-Bromo-4-(4-chlorobenzyl)thiazole-5-carboxamide.

[00500] In a 250 mL round bottomed flask were placed 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylic acid (800 mg, 2 mmol) and toluene (30 mL, 300 mmol). To the suspension was added thionyl chloride (700 uL, 10 mmol) and the mixture was refluxed for 2 h during which time the suspension turned into a solution. The reaction was allowed to cool to rt and then was concentrated under reduced pressure. The residue was co-evaporated with toluene (10 mL). The residual orange oil was dissolved in methylene chloride (30 mL, 500 mmol) then N,N-dimethylaminopyridine (21.2 mg, 0.174) was added. To the mixture was added ammonium hydroxide in water (8.5 M, 20 mL) and the mixture was stirred for 1.5 h at rt. The organic phase was separated and the aqueous phase was extracted with DCM (30 mL). The organic phase and extract were combined and dried over anhydrous MgSO4. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residual yellow syrup was used in the next step without further purification. LC/MS (FA) ES+ 333.

[00501] **Step 8:** (Z)-2-bromo-4-(4-chlorobenzyl)-N-((dimethylamino)methylene)thiazole-5-carboxamide.

[00502] In a 250 mL round bottomed flask were placed 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxamide (0.66 g, 2.0 mmol) and toluene (30 mL, 300 mmol). The mixture was turned into a suspension by ultrasonication. To the suspension was added 1,1-dimethoxy-N,N-dimethylmethanamine (80 uL, 6.0 mmol) and the mixture was stirred for 2 h at 50°C. The mixture was allowed to cool to rt then was concentrated under reduced pressure. The residue was used in the next step without further purification. LC/MS (FA) ES+ 388.

[00503] **Step 9**: 2-Bromo-4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)thiazole.

[00504] In a 250 mL round bottomed flask were placed 2-bromo-4-(4-chlorobenzyl)-N-[(1Z)-(dimethylamino)methylene]-1,3-thiazole-5-carboxamide and acetic acid (50 mL, 900 mmol). Hydrazine hydrate (490 uL, 10 mmol) was added and the mixture was stirred for 1 h at 50°C. The mixture was allowed to cool to rt, then was concentrated under reduced pressure to obtain 3-[2-bromo-4-(4-chlorobenzyl)-1,3-thiazol-5-yl]-4H-1,2,4-triazole as a yellowish off-white crystalline solid. The crude material was used in the next step without further purification. LC/MS (FA) ES+ 357.

[00505] **Step 10:** 2-Bromo-4-(4-chlorobenzyl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiazole

[00506] In a 250 mL round bottomed flask were placed 3-[2-bromo-4-(4-chlorobenzyl)-1,3-thiazol-5-yl]-4H-1,2,4-triazole (0.7 g, 2 mmol) and tetrahydrofuran (50 mL, 600 mmol). To the mixture were added dihydropyran (2 mL, 20 mmol) and p-toluenesulfonic acid monohydrate (911.3 mg, 4.791 mmol). The mixture was refluxed for 2 h then was allowed to cool to rt and then a saturated aqueous solution of $NaHCO_3$ (50 mL) was added. The resulting biphasic mixture was vigorously stirred for 30 min at rt. The aqueous phase was separated then was extracted with EtOAc (50 mL x 2). The combined organic phases were dried over anhydrous $MgSO_4$. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica, elution with a 10%-80% mixture of EtOAc in hexane (linear gradient, 30 min) to afford 3-[2-bromo-4-(4-chlorobenzyl)-1,3-thiazol-5-yl]-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (778 mg; 67% six steps) as a yellow syrup which spontaneously solidified on standing at rt for 2 days. LC/MS (FA) ES+ 441. ^1H NMR (d_6-DMSO, 400 MHz): δ: 8.89 (1H, s), 7.28—7.34 (4H, m), 5.62 (1H, dd, J = 2.8 and 9.6 Hz), 4.52 (2H, s), 3.92—3.96 (1H, m), 3.63—3.70 (1H, m), 1.91—2.14 (3H, m), 1.52—1.72 (3H, m)

[00507] **Step 11:** 4-(4-Chlorobenzyl)-2-(pyridin-4-yl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiazole.

[00508] To a 20 mL vial was added a solution of 3-[2-bromo-4-(4-chlorobenzyl)-1,3-thiazol-5-yl]-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (0.1500 g, 0.3411 mmol) and 4-(tributylstannyl)pyridine (0.2511 g, 0.6822 mmol) in anhydrous 1,4-dioxane (5.000 mL). The solution was degassed for 10 minutes. Lithium chloride (0.108 g, 2.56 mmol) and copper (I) iodide (0.0487 g, 0.256 mmol) were added

followed by tetrakis(triphenylphosphine)palladium(0) (0.0492 g, 0.0426 mmol). The reaction mixture was heated to 90°C and allowed to stir for 18 h. The reaction was cooled to ambient temperature and quenched by the addition of a saturated aqueous solution of sodium bicarbonate (10 mL). The quench mixture was extracted with EtOAc (10 mLx3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica (gradient DCM to 10% MeOH over 30 min) to afford the product (0.2245 g, 73%) as a yellow solid. LC/MS (AA) ES+ 438. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.92 (s, 1H), 7.90 (d, J = 4.8 Hz, 2H), 7.65 (d, J = 1.2 Hz, 2H), 7.38-7.32 (m, 4H), 5.66 (dd, J = 9.6, 2.8 Hz, 1H), 4.65 (s, 2H), 3.97-3.94 (m, 1H), 3.72-3.66 (m, 1H), 1.59-1.48 (m, 2H), 1.32-1.23 (m, 2H), 1.10-1.06 (m, 2H).

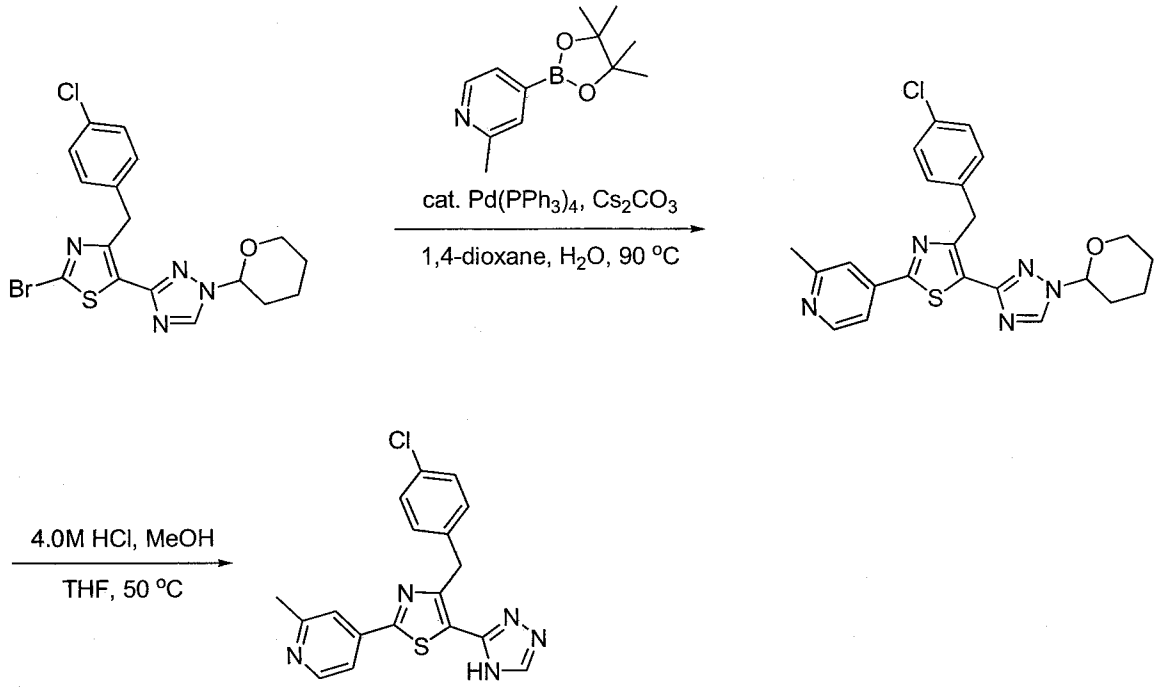
[00509] **Step 12:** 4-(4-Chlorobenzyl)-2-(pyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound **76**).

[00510] To a 20 mL vial was added a solution of 4-{4-(4-chlorobenzyl)-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-1,3-thiazol-2-yl}pyridine (0.2245 g, 0.635 mmol) in anhydrous tetrahydrofuran (2.000 mL) and methanol (2.000 mL). 4.0 M Hydrochloric acid in 1,4-dioxane (1.0 mL, 4.0 mmol) was added and the reaction mixture was allowed to stir at 50°C for 18 hours. The reaction was cooled to ambient temperature and quenched by the addition of a saturated aqueous solution of sodium bicarbonate (10 mL) and extracted with EtOAc (10 mLx3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by HPLC to afford the product (0.0423 g, 45%) as an off white solid. LC/MS (AA) ES+ 354. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 14.48 (s, 1H), 8.71 (dd, J = 4.4, 1.2 Hz, 2H), 7.89-7.87 (m, 2H), 7.38-7.32 (m, 4H), 4.67 (s, 2H).

[00511] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 10:

37	LCMS: (FA) ES+ 372, 374.
39	LCMS: (AA) ES+ 355, 357.
46	LCMS: (AA) ES- 370, 372.
63	LCMS: (FA) ES+ 383, 385.
78	LCMS: (AA) ES+ 372, 374.

[00512] **Example 11: Synthesis of 4-(4-Chlorobenzyl)-2-(2-methylpyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound 18)**



[00513] **Step 1:** 4-(4-chlorobenzyl)-2-(2-methylpyridin-4-yl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiazole.

[00514] To a 20 mL vial was added a solution of 3-[2-bromo-4-(4-chlorobenzyl)-1,3-thiazol-5-yl]-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (0.1000 g, 0.2274 mmol) and 2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine (0.0931 g, 0.425 mmol) in a solution of 1,4-dioxane (2.5000 mL, 32.036 mmol) and water (0.2500 mL). Cesium carbonate (0.2223 g, 0.6822 mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) (0.031533 g, 0.027288 mmol). The reaction mixture was heated to 90°C and allowed to stir for 18 h. The reaction was cooled to ambient temperature and quenched by the addition of a saturated aqueous solution of sodium bicarbonate (10 mL) and extracted with EtOAc (10 mLx3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was dry loaded onto silica gel then was purified by column chromatography on silica (gradient DCM to 10% MeOH over 30 min) to afford the product with Ph_3PO impurities (0.1654 g, 96.6%) as a brown oil. LC/MS (AA) ES+ 452. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.91 (s, 1H), 7.64-7.53 (m, 3H), 7.37-7.31 (m, 4H), 5.66 (dd, J = 9.6, 2.8 Hz, 1H), 4.61 (s, 2H), 3.72-3.66 (m, 2H), 2.55 (s, 3H), 1.70-1.68 (m, 2H), 1.62-1.48 (m, 2H), 1.45-1.38 (m, 2H).

[00515] **Step 2:** 4-(4-Chlorobenzyl)-2-(2-methylpyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound **18**).

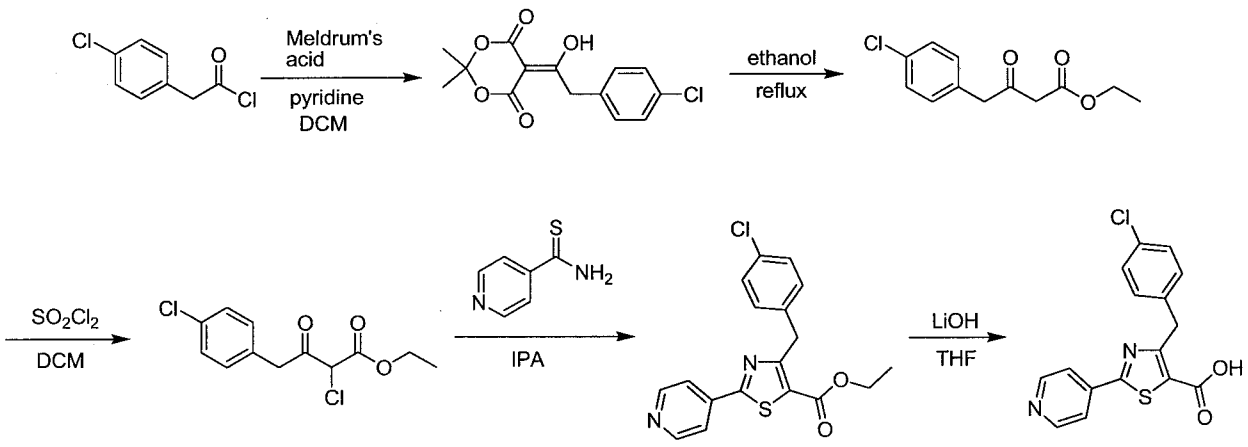
[00516] To a 20 mL vial was added a solution of 4-{4-(4-chlorobenzyl)-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-1,3-thiazol-2-yl}-2-methylpyridine (0.1654 g, 0.365 mmol) in anhydrous tetrahydrofuran (2.000 mL) and methanol (2.000 mL). 4.0 M hydrochloric acid in 1,4-dioxane (1.0 mL, 4.0 mmol) was added and the reaction mixture was allowed to stir at 50°C for 18 hours. The reaction was cooled to ambient temperature and quenched by the addition of a saturated aqueous solution of sodium bicarbonate (10 mL) then was extracted with EtOAc (10 mLx3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by HPLC to afford the product (0.0351 g, 39.9%) as a white solid. LC/MS (AA) ES+ 368, 370. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.73 (s, 1H), 8.56 (d, J = 5.2 Hz, 1H), 7.75 (s, 1H), 7.67 (dd, J = 5.2, 1.6 Hz, 1H), 7.37-7.32 (m, 4H), 4.65 (s, 2H) 2.55 (s, 3H).

[00517] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 11:

137	LCMS: (FA) ES+ 354, 356.
213	LCMS: (FA) ES+ 427.

[00518]

[00519] Example 12: Synthesis of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (Compound 80)



[00520] **Step 1:** 5-(2-(4-Chlorophenyl)-1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione.

[00521] To a mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (52.7 g, 366 mmol) in DCM (205 mL) at -10°C in an ice/methanol bath was added pyridine (72.5 mL, 897 mmol) over 10 minutes. To the resulting solution at -10°C was added a solution of 2-(4-chlorophenyl)acetyl chloride (69.1 g, 366 mmol) in DCM (144 mL) dropwise over 1 hour. The mixture was stirred at -10°C for 1 hour, then at room temperature for

1 hour. The mixture was poured into a mixture of 2 M HCl (820 mL) and ice (400 mL) and the aqueous layer was extracted with DCM (2 x 200 mL). The combined DCM layers were washed with 1 N HCl (100 mL) and brine (100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give 103 g of title compound. (95 % yield). LC/MS (FA) ES- 295. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.25 (br s, 1H), 7.34-7.26 (m, 4H), 4.37 (s, 2H), 1.72 (s, 6H).

[00522] **Step 2:** Ethyl 4-(4-chlorophenyl)-3-oxobutanoate

[00523] A solution of 5-(2-(4-chlorophenyl)-1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (103 g, 347 mmol) in ethanol (718 mL) was refluxed for 3 hours. The reaction was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 0/100→20/80) to give 61 g of the title compound as an orange oil. (73 % yield). LC/MS (FA) ES+ 241. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.28 (m, 2H), 7.15-7.11 (m, 2H), 4.17 (q, 2H, J = 7.2 Hz), 3.81 (s, 2H), 3.45 (s, 2H), 1.26 (t, 3H, J = 7.2 Hz).

[00524] **Step 3:** Ethyl 2-chloro-4-(4-chlorophenyl)-3-oxobutanoate

[00525] To a solution of ethyl 4-(4-chlorophenyl)-3-oxobutanoate (61.0 g, 253 mmol) in DCM (811 mL) in an ice bath was added sulfuryl chloride (34.2 g, 253 mmol) and the resulting solution was allowed to stir at room temperature overnight. The reaction was quenched with saturated sodium bicarbonate solution (200 mL) and the layers separated. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give 70.8 g of title compound. (100 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33-7.30 (m, 2H), 7.17-7.14 (m, 2H), 4.85 (s, 1H), 4.26 (dq, 1H, J = 7.2, 1.2 Hz), 4.02 (d, 1H, J = 16.8 Hz), 3.97 (d, J = 16.8 Hz, 1H), 1.29 (t, 3H, J = 7.2 Hz).

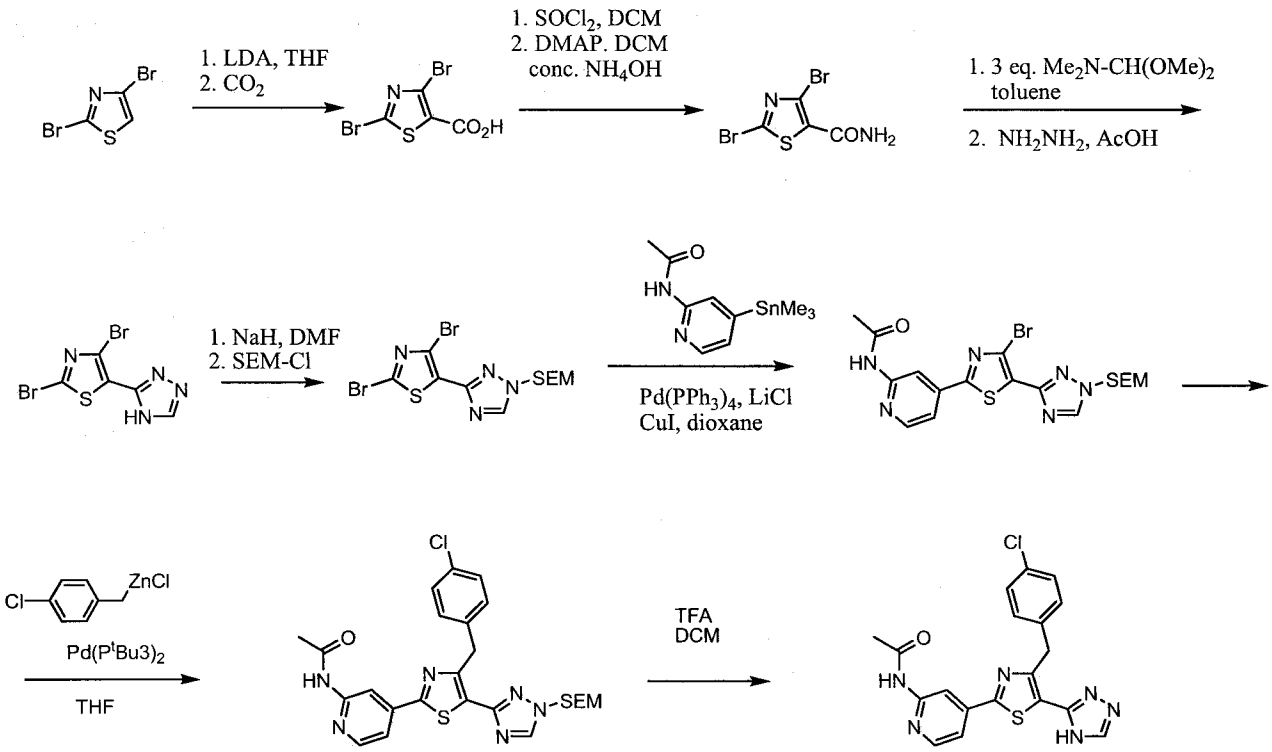
[00526] **Step 4:** Ethyl 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylate

[00527] To a solution of ethyl 2-chloro-4-(4-chlorophenyl)-3-oxobutanoate (70.8 g, 257 mmol) in IPA (2.96 L) was added thioisonicotinamide (71.1 g, 515 mmol) and the resulting mixture was refluxed for 3 days. The reaction was cooled and concentrated in vacuo and the residue was partitioned between DCM (300 ml) and saturated sodium bicarbonate solution (200 mL). The layers were separated and the aqueous layer was extracted with DCM (100 mL). The combined DCM layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude product which was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→40/60) followed by recrystallization from ethyl acetate/hexanes to give 33 g of the title compound as yellow crystals. (36 % yield). LC/MS (FA) ES+ 359. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74-8.72 (m, 2H), 7.81-7.80 (m, 2H), 7.36-7.32 (m, 2H), 7.27-7.23 (m, 2H), 4.54 (s, 2H), 4.38 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz).

[00528] **Step 5:** 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (Compound **80**)

[00529] To a solution of ethyl 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylate (12.8 g, 35.7 mmol) in THF (200 mL) and water (100 mL) was added 1.0 M LiOH (46.4 mL, 46.4 mmol) and the resulting solution was stirred at room temperature overnight. The mixture was acidified to pH 4 with 1 N HCl. The precipitated solids were filtered, washed with water and dried to give 11 g of the title compound as an a white solid. (93 % yield). LC/MS (FA) ES+ 331. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 13.86 (br s, 1H), 8.72-8.71 (m, 2H), 7.89-7.87 (m, 2H), 7.36-7.29 (m, 4H), 4.50 (s, 2H).

[00530] Example 13: Synthesis of *N*-{4-[4-(4-chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (Compound 56)



[00531] **Step 1:** 2,4-Dibromo-1,3-thiazole-5-carboxylic acid:

[00532] To a 500mL 3-neck round bottom flask equipped with dropping funnel and internal temperature monitor was added THF (200 mL) and N,N-diisopropylamine (14.7 mL, 105 mmol) under atmosphere of argon. After cooling at -75°C, 2.50 M of n-Butyllithium in hexane (41.1 mL, 103 mmol) was added dropwise into the solution over 30 min. The internal temperature was kept below -70°C and the resulting solution was stirred for 15 min at -75 °C. To this LDA solution was added a solution of 2,4-dibromothiazole (25.0 g, 99.8 mmol) in THF (60 mL) via dropping funnel over 40 min and the internal

temperature was kept below -70°C, then this solution was stirred for 20 min at -75°C. To this solution was added crushed dry ice at -75°C and the mixture was stirred for 15min. At that time, 10mL water was added dropwise. The cooling bath was removed and the mixture was brought to rt over 1 h with a water bath. The solvent was evaporated under reduced pressure to give a solid residue. The residue was suspended in 100 mL water, basified with 1.00 M of sodium hydroxide in water (110 mL) and extracted with 100 mL ether. The ether layer was washed with 0.5 N NaOH (2 x 30 mL). The combined aqueous solution was acidified with conc. HCl to ~pH 2, extracted with ether (5 x 100 mL, adjusting the pH to ~2 each time after separation). The combined ether solutions were washed with brine, dried over Na_2SO_4, filtered, evaporated to give a solid product (28.04 g, 98%). LCMS: (FA) ES+ 288, ES- 286.

[00533] **Step 2:** 2,4-Dibromo-1,3-thiazole-5-carboxamide:

[00534] A suspension of 2,4-dibromo-1,3-thiazole-5-carboxylic acid (16.33 g, 56.91 mmol) in dry DCM (250 mL) and DMF (0.400 mL) was cooled in an ice bath. Thionyl chloride (40.0 mL, 548 mmol) was added dropwise. The cooling bath was removed and the suspension was stirred at rt for 2.5 hours. Toluene (80 mL, 800 mmol) was added and the suspension was heated to reflux for 1 hour. The mixture was cooled to room temperature, the solvent was removed and the residue was azeotroped with toluene (2 x 100 mL) to give a crude intermediate. This material was suspended in DCM (230 mL) and cooled in an ice bath. N,N-Dimethylaminopyridine (0.70 g, 5.7 mmol) was added, followed by the slow addition of 8.5 M ammonium hydroxide in water (100.0 mL, 850.0 mmol). The mixture was stirred at room temperature overnight. The mixture was filtered and the aqueous layer was separated and extracted with DCM (3 x 100 mL). The combined DCM layers were washed with water, brine, dried over Na_2SO_4, filtered, and evaporated to give a solid product (11.2 g, 69%). LCMS: (FA) ES+ 287 and ES- 285.

[00535] **Step 3:** 3-(2,4-Dibromo-1,3-thiazol-5-yl)-4H-1,2,4-triazole :

[00536] To a suspension of 2,4-dibromo-1,3-thiazole-5-carboxamide (0.110 g, 0.385 mmol) in dry toluene (8.0 mL, 75 mmol) was added DMF-DMA (0.204 mL, 1.54 mmol). The mixture was stirred at 60°C under a nitrogen atmosphere for 3 hours. The solvent was removed and to the intermediate was added acetic acid (2.0 mL, 35 mmol), followed by hydrazine (0.0604 mL, 1.92 mmol). The mixture was heated to 120°C for 30 min. The mixture was cooled to room temperature, the solvent was removed and the residual acetic acid was azeotroped with toluene (2 x 5 mL) to give an oily material, which was basified with saturated aqueous NaHCO3 to pH~8 and extracted with EtOAc (3 x 30 mL). The EtOAc layer was washed with water, brine, dried over Na_2SO_4, filtered, and evaporated to give a crude product. Chromatography on a silica column using EtOAc/hexane (0/100 to 50/50) gave a solid product (0.073 g, 61%). LCMS: (FA) ES+ 311 and ES- 309. ^{1}H NMR (400MHz, d_4-methanol) δ: 8.53 (s, 1H).

[00537] **Step 4:** 3-(2,4-Dbromo-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole

[00538] To the solution of 3-(2,4-dibromo-1,3-thiazol-5-yl)-4H-1,2,4-triazole (1.16 g, 3.74 mmol) in dry DMF (5.0 mL) at 0°C was added portionwise sodium hydride (60%, 0.180 g, 4.49 mmol). The ice bath was removed, mixture was stirred for 5 min at ambient temperature then cooled in an ice bath. [β-(Trimethylsilyl)ethoxy]methyl chloride (0.795 mL, 4.49 mmol) in dry DMF (2.0 mL) was added dropwise and the mixture was stirred at room temperature for 2 hours. The mixture was quenched with ice-water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, evaporated to give a crude oil. The product was purified by column chromatography on silica gel , eluting with EtOAc/hexane (0/100 to 20/80) to afford a white solid product (1.10 g, 67%). LCMS: (FA) ES+ 441. ^{1}H NMR (400MHz, $CDCl_3$) δ: 8.29 (s, 1H), 5.54 (s, 2H), 3.71 (t, J = 8.28 Hz, 2H), 0.95 (t, J = 8.28 Hz, 2H), 0.00 (s, 9H) .

[00539] **Step 5:** N-{4-[4-Bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide:

[00540] The mixture of 3-(2,4-dibromo-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole (1.10 g, 2.50 mmol), N-[4-(trimethylstannyl)pyridin-2-yl]acetamide (0.896 g, 3.00 mmol), tetrakis(triphenylphosphine)palladium (0) (0.155 g, 0.125 mmol), copper(I) iodide (0.143 g, 0.750 mmol) and lithium chloride (0.318 g, 7.50 mmol) in dry 1,4-dioxane (100 mL) was sonicated for 2 min, degassed and backfilled with nitrogen 5 times. The mixture was heated under nitrogen atmosphere to reflux for 90 min, then cooled to room temperature, filtered through celite and washed with dioxane/DCM. The filtrate was evaporated under reduced pressure to give a crude residue, which was purified by column chromatography on silica gel eluting with MeOH/DCM (0/100 to 5/95) to give a product, which was further purified on a silica column using MeOH/EtOAc/hexane (0/0/100 to 5/45/50) to give pure product (0.150 g, 13%). LCMS: (FA) ES+ 495, 497. ^{1}H NMR (400MHz, $CDCl_3$) δ: 8.72 (s, 1H), 8.37 (m, 1H), 8.33 (s, 1H), 8.26 (s, 1H), 7.68 (m, 1H), 5.57 (s, 2H), 3.73 (t, J = 8.28 Hz, 2H), 2.25 (s, 3H), 0.97 (t, J = 8.28 Hz, 2H), 0.00 (s, 9H) .

[00541] **Step 6:** *N*-{4-[4-(4-Chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-5-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00542] To a solution of *N*-{4-[4-bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-5-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.292 g, 0.589 mmol) in tetrahydrofuran (4.1 mL) was added 4-chlorobenzylzinc chloride (0.50M solution in tetrahydrofuran, 2.36 mL, 1.18 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.0226 g, 0.0442 mmol) under argon. The solution was stirred at 60°C for 2 hours. The reaction was incomplete by LCMS, so additional 4-chlorobenzylzinc chloride (0.50M solution in tetrahydrofuran, 2 mL, 1 mmole) was added, then the reaction was stirred at 60°C for an additional 2 hours. The reaction was allowed to cool to room temperature then the solvent was evaporated in vacuo. Column chromatography was performed to yield the title compound (0.112 g,

35%). LCMS: (FA) ES^+, 542. ^1H NMR (400MHz, d_4-methanol) δ: 8.73-8.69 (m, 1 H), 8.42-8.38 (m, 1H), 8.14 (s ,1H), 7.58-7.55 (m, 1H), 7.27-7.20 (m, 4H), 5.52 (s, 2H), 4.32 (s, 2H), 3.68-3.61 (m, 2H), 2.20 (s, 3H), 0.90-0.84 (m, 2H), 0.040 (s, 9H).

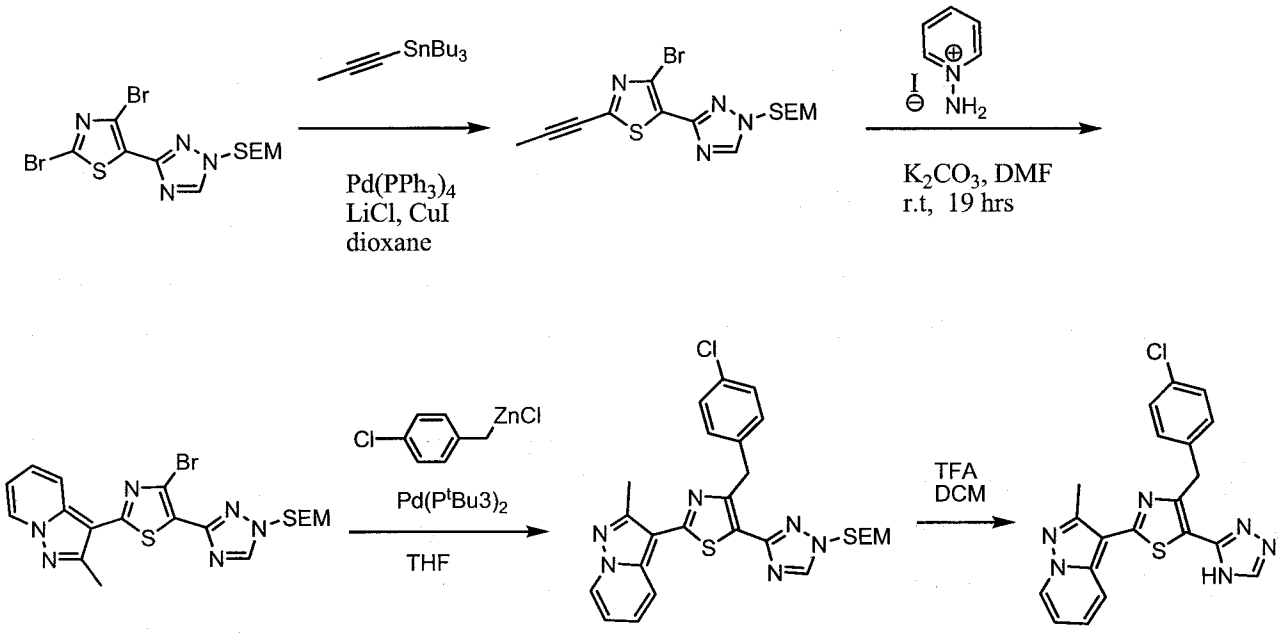
[00543] **Step 7:** *N*-{4-[4-(4-Chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (Compound **56**)

[00544] To a solution of *N*-{4-[4-(4-chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-5-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.112 g, 0.207 mmol) in dichloromethane (2.0 mL) at room temperature was added trifluoroacetic acid (3.1 mL, 40 mmol). The mixture was then stirred at room temperature for 4 hours. The solvent was evaporated and the excess trifluoroacetic acid was removed by azeotroping with toluene. Column chromatography was performed to yield the title compound (0.0520 g, 61%). LCMS: (FA) ES^+, 411. ^1H NMR (400MHz, d_6-DMSO) δ: 14.46 (s, 1H), 10.69 (s, 1H), 8.80-8.73 (m, 1H), 8.64-8.60 (m, 1H), 8.43-8.37 (m, 1H), 7.59-7.54 (m, 1H), 7.37-7.28 (m, 4H), 4.66 (s, 2H), 2.12 (s, 3H).

[00545] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 13:

7	LCMS: (FA) ES+ 388, 390.
27	LCMS: (AA) ES+ 369, 371.
53	LCMS: (AA) ES+ 393, 395.

[00546] **Example 14: Synthesis of 3-[4-(4-chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-*a*]pyridine (Compound 4)**



[00547] **Step 1:** 3-(4-Bromo-2-prop-1-yn-1-yl-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole

[00548] A mixture of 3-(2,4-dibromo-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole (6.00 g, 13.6 mmol), lithium chloride (1.73 g, 40.9 mmol), copper(I) iodide (0.779 g, 4.09 mmol) and tetrakis(triphenylphosphine)platinum (0) (0.848 g, 0.681 mmol) in anhydrous 1,4-dioxane (120 mL, 1500 mmol) was sonicated under an argon atmosphere for 2 minutes in a 250 mL RBF. Tributyl(1-propynyl)tin (4.80 mL, 15.0 mmol) was added. The mixture was heated to 100°C for 1 hour under an argon atmosphere. The mixture was cooled to rt., diluted with DCM (~150 mL), filtered through celite, and washed with DCM. The filtrate was rotavaped to give a crude residue which was then purified by column chromatography (SiO2, elution with 0-100% EtOAc in hexane) to afford a pure solid product (4.14 g, 76 % yield). LCMS: (FA) ES^+ 399, 401. ^1H NMR (400MHz, $CDCl_3$) δ: 8.29 (s, 1H), 5.54 (s, 2H),3.69-3.74 (m, 2H), 2.15 (s, 3H), 0.93-0.97 (m, 2H), 0.00 (s, 9H) .

[00549] **Step 2**: 3-[4-Bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridine

[00550] A mixture of 3-(4-bromo-2-prop-1-yn-1-yl-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole (0.514 g, 1.29 mmol), 1-aminopyridinium iodide (0.343 g, 1.54 mmol) and potassium carbonate (0.231 g, 1.67 mmol) in N,N-dimethylformamide (8.0 mL, 1.0E2 mmol) was stirred at rt for 29 hours. The mixture was quenched with ice water (80 mL) then extracted

with EtOAc 3 times. The combined EtOAc solution was washed with water, brine, dried over Na_2SO_4, filtered and purified by column chromatography (SiO2, elution with 0-100% EtOAc in hexane) to afford a solid product. (0.410 g, 64.8 % yield). LCMS: (FA) ES^+ 491, 493. ^1H NMR (400MHz, $CDCl_3$) δ: 8.43-8.46 (m, 2H), 8.32 (s, 1H), 7.39-7.42 (m, 1H), 6.90-6.93 (m, 1H), 5.57 (m, 2H), 3.72-3.76 (m, 2H), 2.76 (s, 3H), 0.96-1.00 (m, 2H),0.00 (s, 9H) .

[00551] **Step 3:** 3-[4-(4-Chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-*a*]pyridine

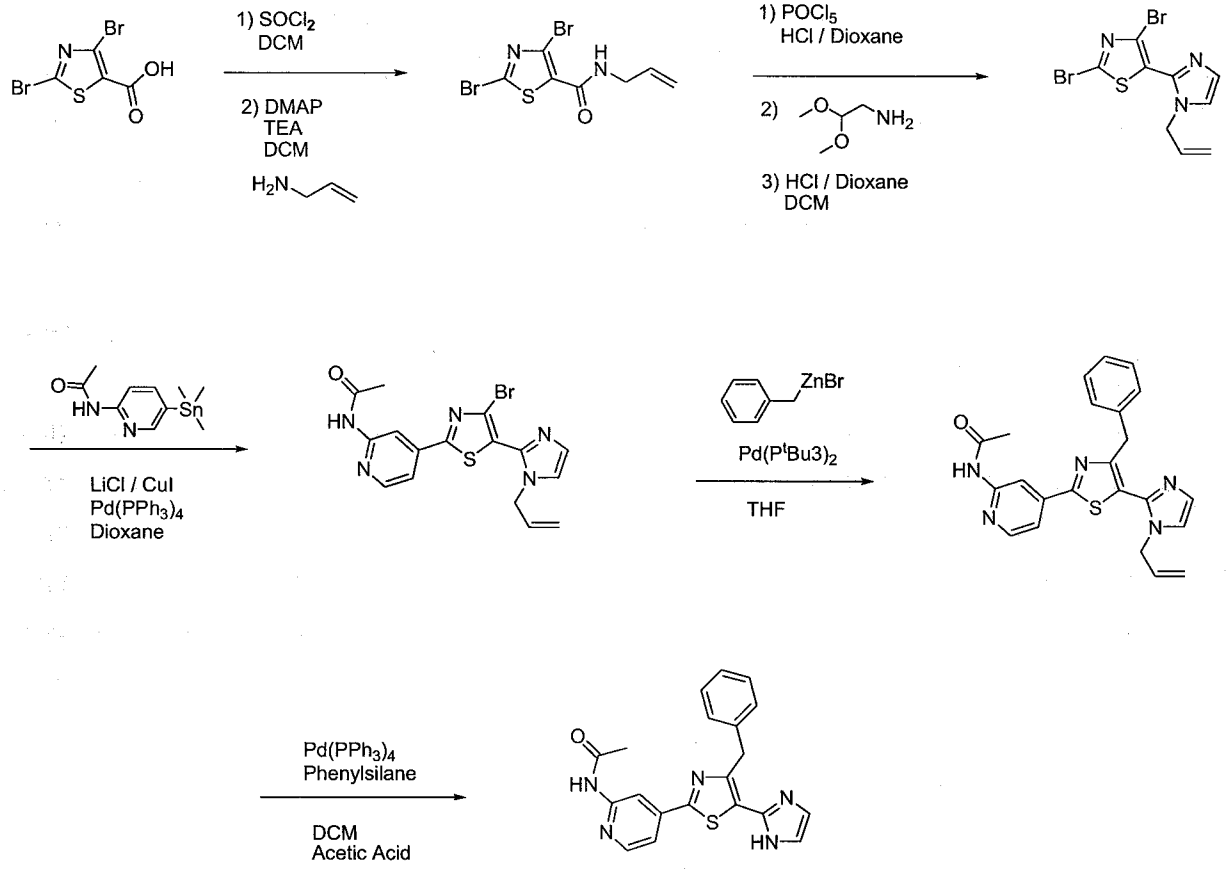
[00552] To a solution of 3-[4-bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-*a*]pyridine (0.200 g, 0.407 mmol) in tetrahydrofuran (2.8 mL) were added 4-chlorobenzylzinc chloride (0.50M solution in tetrahydrofuran, 1.63 mL, 0.814 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.0156 g, 0.0305 mmol) under argon. The solution was stirred at 60°C for 3 hours. The reaction was incomplete by LCMS, so additional 4-chlorobenzylzinc chloride (0.50M solution in tetrahydrofuran, 1.0 mL, 0.5 mmole) was added then the reaction was stirred at 60°C for an additional 3 hours. The reaction was cooled to room temperature then the solvent was evaporated in vacuo. The residue was purified by column chromatography (SiO2, elution with EtOAc in hexanes 10-100% gradient) to yield the title compound (0.188 g, 86%). LCMS: (FA) ES^+, 538. ^1H NMR (400MHz, d_6-DMSO) δ: 8.87 (s, 1 H), 8.76-8.72 (m, 1H), 8.28-8.24 (m,1H), 7.54-7.48 (m, 1H), 7.44-7.40 (m, 2H), 7.35-7.30 (m, 2H), 7.09-7.03 (m, 1H), 5.58 (s, 2H), 4.63 (s, 2H), 3.68-3.62 (m, 2H), 2.66 (s, 3H), 0.91-0.84 (m, 2H), 0.050 (s, 9H).

[00553] **Step 4:** 3-[4-(4-Chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-*a*]pyridine (Compound **4**)

[00554] To a solution of 3-[4-(4-chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-*a*]pyridine (0.182 g, 0.339 mmol) in dichloromethane (3.3 mL) at room temperature was added trifluoroacetic acid (5.1 mL, 66 mmol). The mixture was then stirred at room temperature for 3 hours. The solvent was evaporated and the excess trifluoroacetic acid was removed by azeotroping with toluene. The crude product was purified by column chromatography (SiO2, elution with hexane to 100% ethyl acetate) to yield the title compound (0.0884 g, 64%). LCMS: (FA) ES^+, 407. ^1H NMR (400MHz, d_6-DMSO) δ: 8.76-8.70 (m, 2H), 8.28-8.22 (m, 1H), 7.53-7.46 (m, 1H), 7.45-7.40 (m, 2H), 7.37-7.31 (m, 2H), 7.07-7.01 (m, 1H), 5.55-5.50 (m, 1H), 4.64 (s, 2H), 2.65 (s, 3H).

[00555] **Example 15: Synthesis of N-{4-[4-benzyl-5-(1H-imidazol-2-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (Compound 2)**

[00556]



[00557] **Step 1:** *N*-allyl-2,4-dibromo-1,3-thiazole-5-carboxamide

[00558] To a solution of 2,4-dibromo-1,3-thiazole-5-carboxylic acid (25.0 g, 87.1 mmol) in dichloromethane (600 mL) at 0°C was added thionyl chloride (66.1 mL, 906 mmol) followed by N,N-dimethylformamide (7.02 mL, 90.6 mmol). The mixture was allowed to warm to room temperature and stir for 2 hours. The solvent was evaporated and the excess thionyl chloride was removed by azeotroping with toluene. The residue was dissolved in dichloromethane (600 mL) and cooled to 0°C, then added triethylamine (63.2 mL, 453 mmol) was added followed by 2-propen-1-amine (23.8 mL, 317 mmol) and N,N-dimethylaminopyridine (1.11 g, 9.06 mmol). The mixture was allowed to warm to room temperature and stirred for 2 hours. The solution was then diluted with dichloromethane and water and the layers were separated. The aqueous phase was then extracted with dichloromethane twice, then the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield the title compound (14.3 g, 50%). LCMS: (FA) ES^+, 327. ^1H NMR (400MHz, d_4-methanol) δ: 5.97-5.85 (m, 1H), 5.32-5.24 (m, 1H), 5.20-5.14 (m, 1H), 4.02-3.95 (m, 2H).

[00559] **Step 2:** 5-(1-allyl-1*H*-imidazol-2-yl)-2,4-dibromo-1,3-thiazole

[00560] To a solution of *N*-allyl-2,4-dibromo-1,3-thiazole-5-carboxamide (13.0 g, 39.9 mmol) in dichloromethane (260 mL) was added phosphorus pentachloride (9.93 g, 47.7 mmol) and 4M hydrochloric acid in dioxane (1.52 mL, 6.06 mmol). The reaction was heated to 60°C for 90 minutes under an atmosphere on nitrogen. The reaction was allowed to cool to room temperature and then aminoacetaldehyde dimethyl acetal (47.8 mL, 439 mmol) was added slowly through the condenser. The mixture was heated to 60°C for 2 hours under an atmosphere of nitrogen then cooled to room temperature, and water was added (200 mL). The layers were separated and the organic phase was washed with water again (2 x 200 mL). The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and washed with dichloromethane (200 mL). To this dichloromethane solution of the intermediate was added 4M hydrochloric acid in dioxane (120 mL, 480 mmol) and the solution was stirred at 60°C for 16 hours. The solution was decanted (leaving behind an oily black residue on the flask) then the solvent was evaporated and the residue was diluted with ethyl acetate and saturated sodium bicarbonate solution. The layers were separated and the aqueous phase was extracted three more times with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield the title compound (8.04 g, 58%). LCMS: (FA) ES^+, 306 (parent minus allyl group). ^1H NMR (300MHz, d_4-methanol) δ: 7.37-7.31 (m, 1H), 7.20-7.16 (m, 1H), 6.02-5.86 (m, 1H), 5.26-5.18 (m, 1H), 5.07-4.96 (m, 1H), 4.68-4.59 (m, 2H).

[00561] **Step 3:** Synthesis of *N*-{4-[5-(1-allyl-1*H*-imidazol-2-yl)-4-bromo-1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00562] To a solution of 5-(1-allyl-1*H*-imidazol-2-yl)-2,4-dibromo-1,3-thiazole (5.00 g, 14.3 mmol) in 1,4-dioxane (133 mL) was added N-[4-(trimethylstannyl)pyridine-2-yl]acetamide (5.14 g, 17.2 mmol), lithium chloride (1.82 g, 43.0 mmol), copper (I) iodide (0.818 g, 4.30 mmol) and tetrakis (triphenylphosphine)palladium(0) (1.24 g, 1.07 mmol). The flask was purged with argon and then the mixture was heated at 115 °C for 4 hours. The reaction was allowed to cool to room temperature, and then the solvent was evaporated in vacuo. Column chromatography was performed to yield the title compound (3.13 g, 54%). LCMS: (FA) ES^+, 406. ^1H NMR (400MHz, d_6-DMSO) δ: 10.77 (s, 1H), 8.66-8.61 (m, 1H), 8.49-8.44 (m, 1H), 7.61-7.56 (m, 1H), 7.49-7.45 (m, 1H), 5.98-5.87 (m, 1H), 5.19-5.12 (m, 1H), 4.95-4.88 (m, 1H), 4.70-4.64 (m, 2H), 2.13 (s, 3H).

[00563] **Step 4:** Synthesis of N-{4-[5-(1-allyl-1H-imidazol-2-yl)-4-benzyl-1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00564] To a solution of *N*-{4-[5-(1-allyl-1*H*-imidazol-2-yl)-4-bromo-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.0500 g, 0.124 mmol) in tetrahydrofuran (0.86 mL) was added benzylzinc bromide

(0.50M solution in tetrahydrofuran, 0.495 mL, 0.247 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.00474 g, 0.00928 mmol) under argon. The solution was stirred at 60°C for 2 hours then cooled to room temperature. The solvent was evaporated in vacuo. Column chromatography was performed to yield the title compound (0.0110 g, 21%). LCMS: (FA) ES^+, 416. ^1H NMR (400MHz, d_4-methanol) δ: 8.70-8.65 (m, 1 H), 8.41-8.36 (m, 1H), 7.66-7.61 (m ,1H), 7.34-7.05 (m, 7H), 5.81-5.70 (m, 1H), 5.16-5.10 (m, 1H), 4.95-4.88 (m, 1H), 4.38-4.33 (m, 2H), 4.13 (s, 2H), 2.20 (s, 3H).

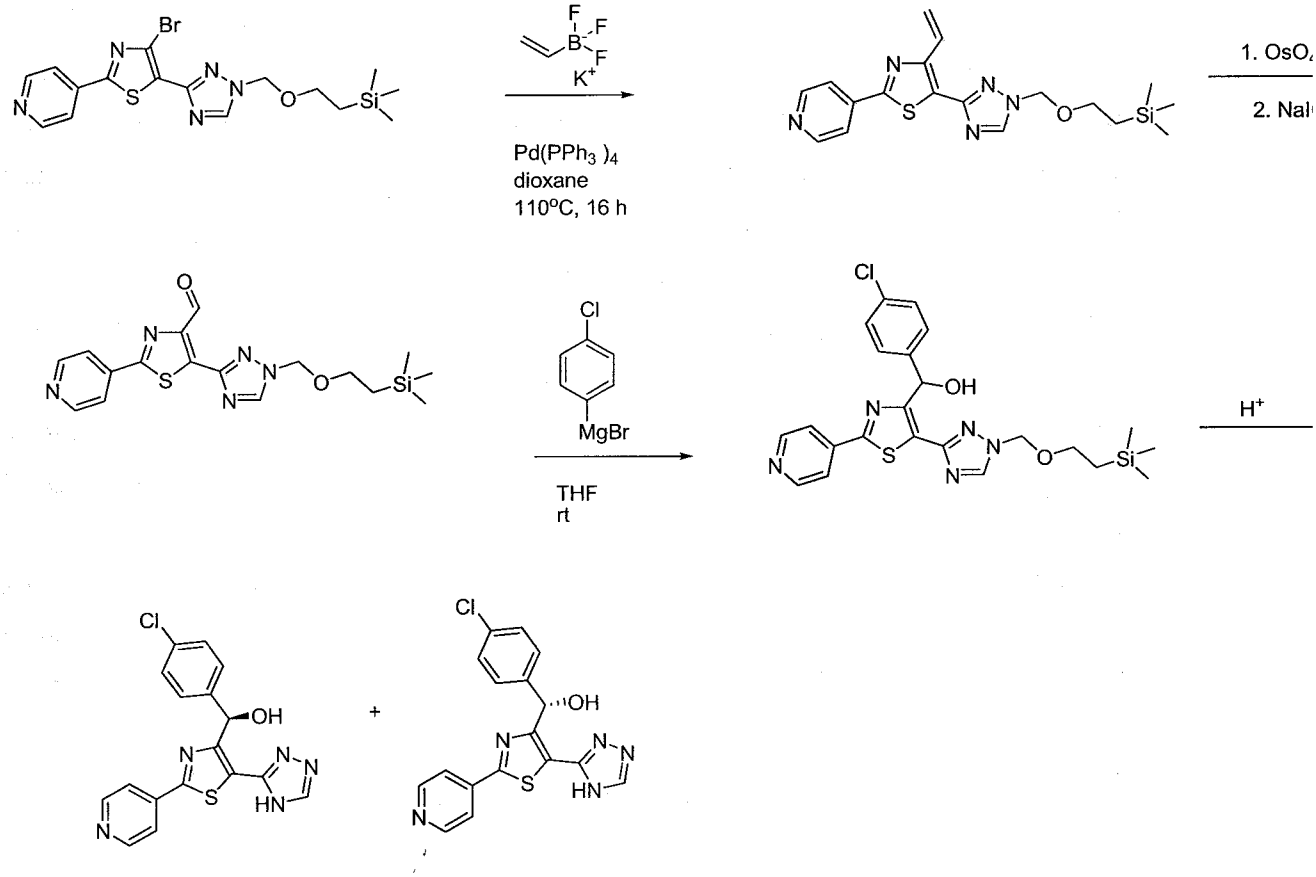
[00565] **Step 5:** Synthesis of N-{4-[4-benzyl-5-(1H-imidazol-2-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (Compound **2**)

[00566] To a solution of N-{4-[5-(1-allyl-1H-imidazol-2-yl)-4-benzyl-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.210 g, 0.0505 mmol) in dichloromethane (0.38 mL) and acetic acid (0.13 mL) was added tetrakis (triphenylphosphine)palladium(0) (0.00292 g, 0.00253 mmol) followed by phenylsilane (0.0318 mL, 0.258 mmol). The solution was stirred at 40°C for 3 hours. The solution was cooled to room temperature then concentrated in vacuo and diluted with ethyl acetate and saturated sodium bicarbonate solution. The layers were separated and the aqueous phase was extracted three more times with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield the title compound (0.0100 g, 53%). LCMS: (FA) ES^+, 376. ^1H NMR (400MHz, d_4-methanol) δ: 8.67-8.63 (m, 1H), 8.38-8.35 (m, 1H), 7.63-7.59 (m, 1H), 7.25-7.07 (m, 7H), 4.42 (s, 2H), 2.20 (s, 3H).

[00567] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 15:

24	LCMS: (FA) ES+ 390
67	LCMS: (FA) ES+ 410, 412.
73	LCMS: (FA) ES+ 410, 412.

[00568] **Example 16: Synthesis of (4-chlorophenyl)[2-pyridin-4-yl-5-(1H-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]methanol (Compounds 19 and 70)**



[00569] **Step 1:** 4-[5-(1-{[2-(Trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-4-vinyl-1,3-thiazol-2-yl]pyridine.

[00570] Into a sealed tube was added potassium vinyltrifluoroborate (1.34 g, 10.0 mmol), 1,4-dioxane (21.0 mL, 269 mmol), 4-[4-bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]pyridine (2.0 g, 4.6 mmol) and 2 M sodium carbonate in water (9.10 mL, 18.2 mmol). The reaction was degassed with nitrogen for 15 min then tetrakis(triphenylphosphine)palladium(0) (527 mg, 0.456 mmol) was added. The tube was sealed and the reaction was heated in an oil bath at 110°C with stirring overnight. The reaction solution was cooled to room temperature, water (10 mL) and EtOAc (10 mL) were added, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2, elution with 0-10 % MeOH in DCM) to give the title compound as a yellow solid (1.34 g 81%). LCMS: (FA) ES^+, 386. ^1H NMR (400 MHz, *d6*-DMSO) δ:8.92 (s, 1H), δ 8.74-8.76 (dd, J = 1.75 Hz, J = 1.5 Hz 2H), 7.96-7.98 (dd, J = 1.75 Hz, 2H), 6.34-6.40 (dd, J = 2.3 Hz, 1 2H), 5.62-5.65 (dd, J = 2.3 Hz, 1H), 5.60 (s, br, 2H), 3.63-3.68 (m, 2H), 0.86-0.90 (m, 2H), -0.04 (s, 9H).

[00571] **Step 2:** 2-Pyridin-4-yl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazole-4-carbaldehyde

[00572] To a solution of 4-[5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-4-vinyl-1,3-thiazol-2-yl]pyridine (1.43 g, 2.60 mmol) in a 3:1 mixture of 1,4-dioxane (17.5 mL, 224.6 mmol) and water (5.8 mL, 324.25 mmol) was added 2,6-lutidine (1.50 mL, 12.98 mmol) and the mixture was cooled to 0°C. Sodium metaperiodate (2.80 g, 12.98 mmol) was added followed by the addition of 4% osmium tetroxide in water (0.50 mL, 0.080 mmol) and the reaction mixture was slowly warmed to ambient temperature and allowed to stir overnight. Water (10mL) was added. The resulting yellow precipitate was collected by filtration, washed with water, ether and MeOH. The filtrate was concentrated under reduced pressure and dried on the high vac to give the title compound (1.0g, yield 99%). LCMS: (FA) ES^+, 388. ^1H NMR (400 MHz, d_6-DMSO) δ: 10.70(s, 1H), δ:9.05 (s, 1H), 8.79-8.80 (dd, J = 1.5 Hz, 2H), 7.98-8.0 (dd, J = 1.5 Hz, J = 1.7 Hz, 2H), 5.64-5.66 (s, br, 2H), 3.64-3.68 (m, 2H), 0.870-0.90(m, 2H), -0.03 (s, 9H).

[00573] **Step 3:** (4-Chlorophenyl)[2-pyridin-4-yl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]methanol

[00574] To a solution of 2-pyridin-4-yl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazole-4-carbaldehyde (280.0 mg, 0.722 mmol) in tetrahydrofuran (4.0 mL, 40 mmol), 1 M 4-chlorophenyl magnesium bromide in ether (4.0 mL, 4 mmol) was added and the mixture was stirred for 40 min at rt. After the reaction was completed a 5% aqueous solution of NH_4Cl (10 mL) and EtOAc (10 mL) were added and the resulting bi-phasic mixture was vigorously stirred for 15 min then the aqueous phase was discarded. The organic phase was washed with brine (5 mL) then dried over anhydrous $MgSO_4$. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2, elution with 20-80 % EtOAc in hexane) to give the title compound as a white solid (230 mg, 73.6%). LCMS: (FA) ES^+, 500. ^1H NMR (400 MHz, d_6-DMSO) δ:8.96 (s, 1H), δ 8.70-8.72 (dd, J = 1.75 Hz, 2H), 7.87-7.89 (dd, J = 1.75, 2H), 7.32-7.37(m, 2H), 7.55-7.58(m, 3H), 6.85-6.87(d, J = 5.5 Hz , 1H) , 6.15-6.17(d, J = 5.5 Hz , 1H) , 5.6 (s, br, 2H), 3.65-3.67 (m, 2H), 0.850-0.90(m, 2H), -0.05 (s, 9H).

[00575] **Step 4:** (4-Chlorophenyl)[2-pyridin-4-yl-5-(1H-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]methanol.

[00576] (4-Chlorophenyl)[2-pyridin-4-yl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]methanol(266.0 mg, 0.530 mmol) was dissolved in methylene chloride (3.0 mL, 47 mmol). Trifluoroacetic acid (3.0 mL, 39 mmol) was added and the solution was stirred at rt overnight. After the reaction wass completed, saturated $NaHCO_3$ was added and the reaction was stirred at rt for 20 min, then EtOAc (5mL) was added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, concentrated and the obtained residue was purified by column chromatography (SiO_2, elution with 2-20% MeOH in DCM) to give the title compound as a white solid (200 mg). The racemic isomers were separated by chiral prep HPLC to yield **17** (34 mg, 12.7%) (peak 1, ret. time 13.04 min).

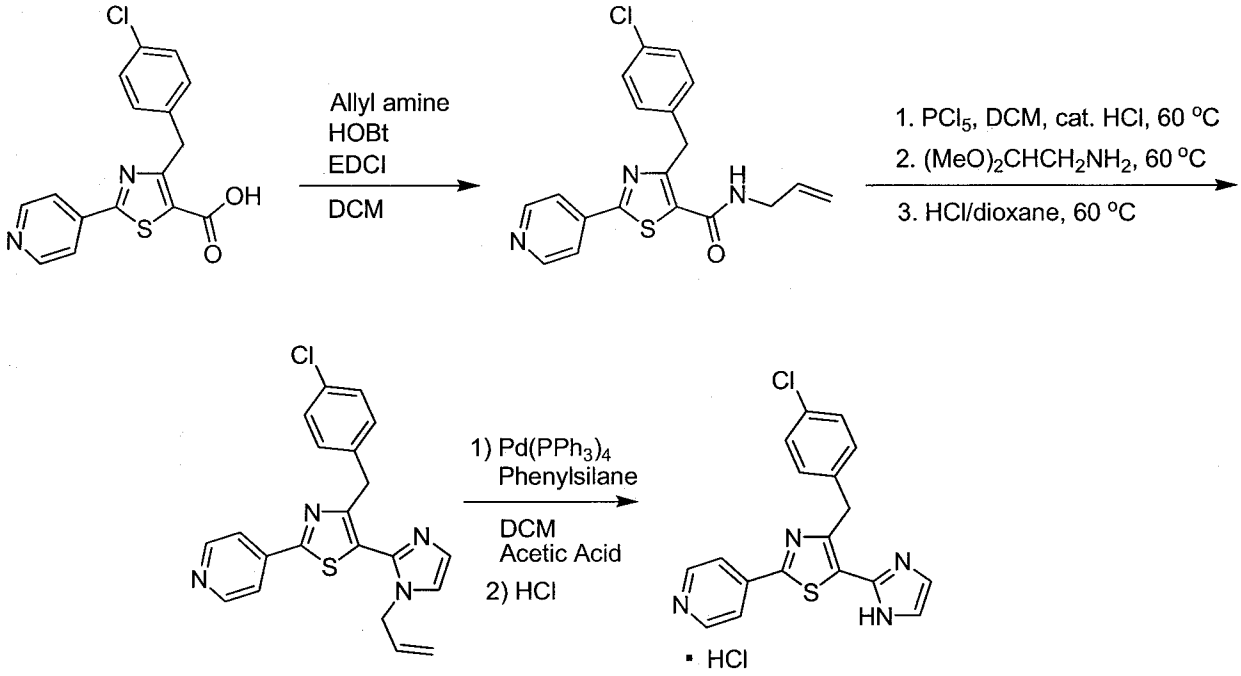
LCMS: (FA) ES^+, 370. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.76(s, 1H), 8.69-8.71 (dd, J = 1.5 Hz, 2H), 7.86-7.88 (dd, J = 1.5, 2H), 7.55-7.58(d, , J = 8.5 Hz, 2H), 7.34-7.38(d, J = 8.5 Hz, 2H), 6.84-6.86 (s, br, 1H) and **70** (34.8 mg, 13.0%) (peak 2, ret. time 13.2 min). LCMS: (FA) ES^+, 370. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.68-8.72(m, 3H), 7.86-7.88 (dd, J = 1.69 Hz , J = 1.5 Hz , 2H), 7.54-7.58(d, , J = 8.47 Hz, 2H), 7.34-7.38(d, J = 8.47 Hz, 2H), 6.81-6.82 (s, br, 1H).

[00577] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 16:

149	LCMS: (AA) ES+ 451, 453, 455
168	LCMS: (FA) ES+ 418, 420
238	LCMS: (AA) ES+ 427, 429
265	LCMS: (AA) ES+ 431, 433
278	LCMS: (AA) ES+ 451, 453, 455
282	LCMS: (FA) ES+ 418, 420
285	LCMS: (AA) ES+ 431, 433

[00578]

[00579] Example 17: Synthesis of 4-(4-chlorobenzyl)-5-(1H-imidazol-2-yl)-2-(pyridin-4-yl)thiazole (Compound 15)



[00580] **Step 1:** N-Allyl-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxamide

[00581] To a stirred solution of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (220 mg, 0.665 mmol) in DCM (4.05 mL) was added HOBT (98.8 mg, 0.732 mmol) and EDCI (204 mg, 1.06 mmol) at room temperature and the mixture was stirred for 30 min. To the solution was added 2-propen-1-amine (0.200 mL, 2.66 mmol) then the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM (10 mL) and washed with water (3 mL) and brine (2 mL), then dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→75/25) to give 150 mg of the title compound as a yellow solid (61 % yield). LC/MS (FA) ES+ 370. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74-8.72 (m, 2H), 7.79-7.77 (m, 2H), 7.35-7.32 (m, 2H), 7.27-7.25 (m, 2H), 5.94-5.80 (m + bs, 2H), 5.25-5.20 (m, 2H), 4.48 (s, 2H), 4.06-4.02 (m, 2H).

[00582] **Step 2:** 5-(1-Allyl-1H-imidazol-2-yl)-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole

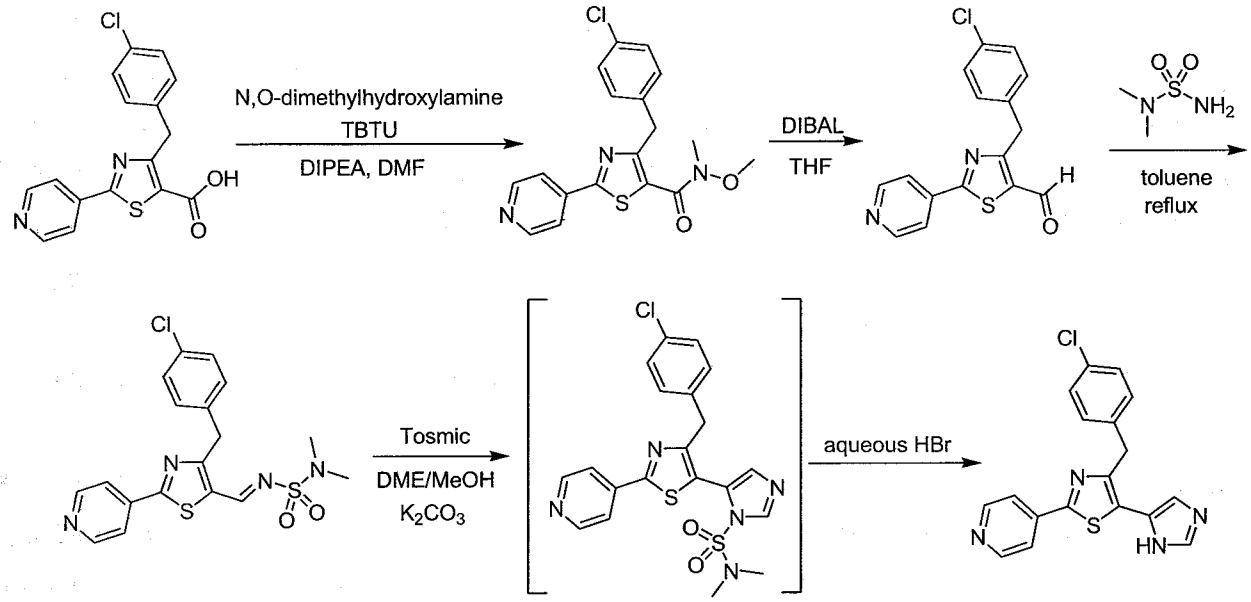
[00583] To a solution of N-allyl-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxamide (150 mg, 0.406 mmol) in DCM (2.64 mL) was added phosphorus pentachloride (101 mg, 0.485 mmol) and 4 M hydrochloric acid in 1,4-dioxane (0.0154 mL, 0.0614 mmol) and the mixture was heated to 60 °C for 1.5 h. The reaction was cooled to room temperature and aminoacetaldehyde dimethyl acetal (0.486 mL, 4.46 mmol) was added. The resulting mixture was heated at 60°C for 2 h. The mixture was cooled to room temperature, diluted with DCM (10 mL), washed with water (2 x 2 mL) and brine (2 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was taken up in DCM (3.0 mL) and 4 M hydrochloric acid in 1,4-dioxane (0.608 mL, 2.43 mmol) was added and the mixture was stirred at 60°C

overnight. The reaction was cooled and concentrated in vacuo. The residue was taken up in ethyl acetate (20 mL) and saturated sodium bicarbonate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (methanol/DCM = 0/100→5/95) to give 99 mg of the title compound (62 % yield). LC/MS (FA) ES+ 393. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.72-8.70 (m, 2H), 7.80-7.72 (m, 2H), 7.26 (m, 1H), 7.22-7.14 (m, 4H), 7.06 (m, 1H), 5.84-5.71 (m, 1H), 5.23-5.19 (m, 1H), 5.01-4.96 (m, 1H), 4.38-4.34 (m, 2H), 4.20 (s, 2H).

[00584] **Step 3:** 4-(4-Chlorobenzyl)-5-(1H-imidazol-2-yl)-2-(pyridin-4-yl)thiazole, hydrochloride salt (Compound **15**)

[00585] To a solution of 5-(1-allyl-1H-imidazol-2-yl)-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole (99.0 mg, 0.252 mmol) and tetrakis(triphenylphosphine)palladium (14.6 mg, 0.0126 mmol) in DCM (3.38 mL) was added acetic acid (0.623 mL, 11.0 mmol) and phenylsilane (0.158 mL, 1.28 mmol) and the mixture was stirred for 2 h at 40°C. The reaction mixture was evaporated to remove volatiles and DCM (10 mL) added. To this solution was added saturated sodium bicarbonate (4 mL) and the resulting mixture was stirred for 30 min. The mixture was extracted with DCM (3 x 10 mL) and the combined DCM layers were washed with brine. The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (methanol/DCM = 0/100→10/90) to give 57 mg of the title compound as a yellow solid (64 % yield). The HCl salt was made as follows. To a mixture of the free base (57 mg, 0.162 mmol) in ethanol (5 mL) was added 1.0 M HCl in ether (0.178 mL, 0.178 mmol) and the mixture was stirred for 2 hours then concentrated in vacuo. The residue was taken up in a minimum of methanol, and acetonitrile was added to give a precipitate. Ether was added and the precipitate was filtered, washed with ether and dried to give the title compound as an orange solid. LC/MS (FA) ES+ 353. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.78-8.74 (m, 2H), 7.96-7.91 (m, 2H), 7.48-7.43 (m, 2H), 7.34-7.28 (m, 4H), 4.51 (s, 2H).

[00586] **Example 18: Synthesis of 4-(4-chlorobenzyl)-5-(1H-imidazol-5-yl)-2-(pyridin-4-yl)thiazole (Compound 66)**



[00587] **Step 1:** 4-(4-Chlorobenzyl)-N-methoxy-N-methyl-2-(pyridin-4-yl)thiazole-5-carboxamide

[00588] To a solution of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (850 mg, 2.57 mmol) in DMF (11.9 mL) was added N,O-dimethylhydroxylamine hydrochloride (852 mg, 8.74 mmol), HATU (1.95 g, 5.14 mmol) and diisopropylethylamine (2.42 mL, 13.9 mmol) and the resulting solution was stirred at room temperature overnight. The reaction was diluted with water (30 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with water (3 x 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→80/20) to give 775 mg of the title compound as a yellow solid (80 % yield). LC/MS (FA) ES+ 374. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72-8.70 (m, 2H), 7.84-7.82 (m, 2H), 7.37-7.34 (m, 2H), 7.25-7.22 (m, 2H). 4.56 (s, 2H), 3.70 (s, 3H), 3.37 (s, 3H).

[00589] **Step 2:** Preparation of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carbaldehyde

[00590] To a solution of 4-(4-chlorobenzyl)-N-methoxy-N-methyl-2-(pyridin-4-yl)thiazole-5-carboxamide (1.13 g, 3.02 mmol) in THF (36.8 mL) at -50°C was added 1.0 M diisobutylaluminum hydride in hexane (15.1 mL, 15.1 mmol) and the resulting solution was stirred at -50°C to -30°C for 2 hours. The reaction was quenched with saturated ammonium chloride (10 mL) and allowed to warm to room temperature. Water (25 mL) was added and the mixture was extracted with ethyl acetate (2 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→70/30) to give 699 mg of the title compound as a white solid (73 % yield). LC/MS (FA) ES+ 315. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.16 (s, 1H), 8.78-8.76 (m, 2H), 7.85-7.83 (m, 2H), 7.30-7.25 (m, 4H), 4.47 (s, 2H).

[00591] **Step 3:** N'-{(1E)-[4-(4-chlorobenzyl)-2-pyridin-4-yl-1,3-thiazol-5-yl]methylene}-N,N-dimethylsulfamide

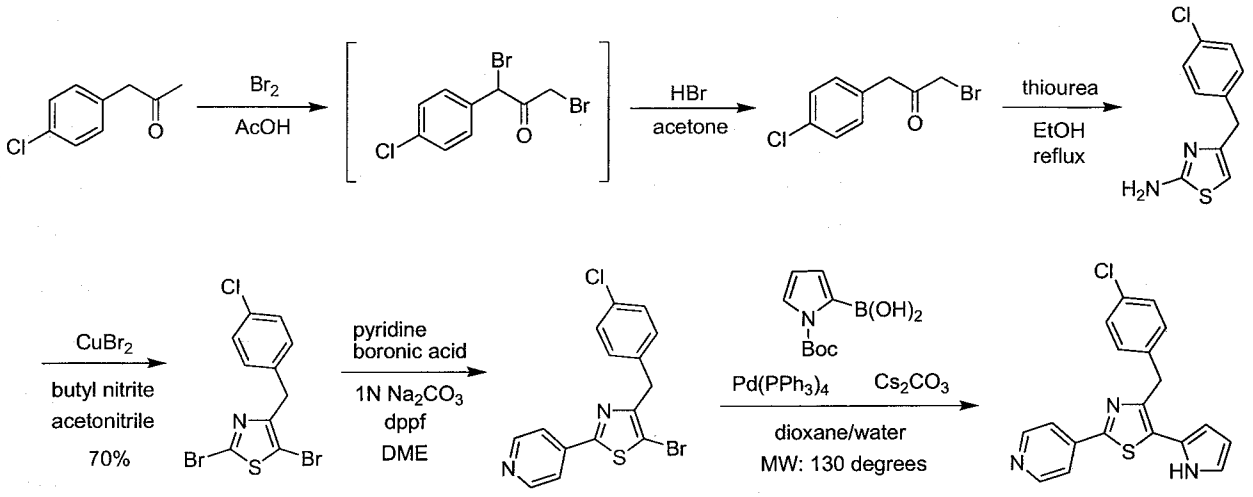
[00592] A solution of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carbaldehyde (186 mg, 0.591 mmol) and N,N-dimethylsulfonamide ((75.6 mg, 0.608 mmol) (prepared according to Li, *Tetrahedron Letters*, 50(19), 2232-2235) in toluene (5.0 mL) was refluxed overnight using a Dean Stark trap to azeotrope water. The reaction was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→60/40) to give 699 mg of the title compound as a yellow solid (60% yield). LC/MS (FA) ES+ 421. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.08 (s, 1H), 8.78-8.76 (m, 2H), 7.84-7.82 (m, 2H), 7.32-7.22 (m, 4H), 4.38 (s, 2H), 2.86 (s, 6H).

[00593] **Step 4:** 5-(4-(4-Chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide and 4-(4-chlorobenzyl)-5-(1H-imidazol-5-yl)-2-(pyridin-4-yl)thiazole (Compound **66**).

[00594] A solution of N'-{(1E)-[4-(4-chlorobenzyl)-2-pyridin-4-yl-1,3-thiazol-5-yl]methylene}-N,N-dimethylsulfamide (148 mg, 0.352 mmol), p-tolylsulfonylmethyl isocyanide (75.5 mg, 0.387 mmol) and potassium carbonate (146 mg, 1.05 mmol) in DME (2.50 mL) was heated at 78°C for 2 hours. The reaction was diluted with DCM (10 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with DCM (5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (methanol/DCM = 0/100→15/85) to give 50 mg of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide. LC/MS (FA) ES+ 460. (Some of the deprotected product, 4-(4-chlorobenzyl)-5-(1H-imidazol-5-yl)-2-(pyridin-4-yl)thiazole, was also obtained (19 mg). This material was combined with the material obtained in the following deprotection step.)

A solution of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (50 mg, 0.109 mmol) in 48% HBr in water (3.0 mL) was heated to 90°C for 2.5 hours. The cooled solution was taken up in DCM (20 mL) and saturated sodium bicarbonate (20 mL). The layers were separated and the aqueous extracted with DCM (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. To this crude material was added the 19 mg of deprotected material obtained in the previous step. The combined material was purified by silica gel chromatography (methanol/DCM = 0/100→15/85) to give 34 mg of the title compound as a white solid (27 % yield). LC/MS (FA) ES+ 353. ^{1}H NMR (300 MHz, d_4-MeOH) δ: 8.63-8.61 (m, 2H), 7.93-7.91 (m, 2H), 7.80 (d, 1H, J = 1.1 Hz), 7.30-7.19 (m, 5H), 4.35 (s, 2H).

[00595] **Example 19: Synthesis of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)-5-(1H-pyrrol-2-yl)thiazole (Compound 22)**



[00596] **Step 1:** 1-Bromo-3-(4-chlorophenyl)propan-2-one

[00597] To a solution of 1-(4-chlorophenyl)propan-2-one (25.0 g, 148 mmol) in acetic acid (37.9 mL) was added 48% aqueous HBr (19.0 mL, 168 mmol). A solution of bromine (16.3 mL, 316 mmol) in acetic acid (63.2 mL) was then added over 10 minutes and the resulting solution was stirred for 4 hours at room temperature. Acetone (190 mL) was added and the resulting solution was stirred at room temperature for 3 days. The reaction was concentrated in vacuo and the residue was taken up in DCM (300 mL) and brine (100 mL). The layers were separated and the aqueous layer was extracted with DCM (100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/hexanes = 0/100→15/85) to give 25.4 grams of the title compound as a dark gray solid (69 % yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.31 (m, 2H), 7.18-7.15 (m, 2H), 3.94 (s, 2H), 3.91 (2, 2H).

[00598] **Step 2:** 4-(4-Chlorobenzyl)thiazol-2-amine

[00599] A mixture of 1-bromo-3-(4-chlorophenyl)propan-2-one (25.4 grams, 103 mmol) and thiourea (8.59 g, 113 mmol) in ethanol (1.51 L) was heated at 85°C for 2 hours. The reaction was cooled and concentrated in vacuo and the residue was taken up in ethyl acetate (300 mL) and saturated sodium bicarbonate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was recrystallized from ethyl acetate/hexanes to give 19.9 grams of the title compound as a tan powder (86 % yield). LC/MS (FA) ES+ 225. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.29-7.24 (m, 2H), 7.20-7.15 (m, 2H), 6.04 (m, 1H), 5.00 (bs, m, 2H), 3.83 (s, 2H).

[00600] **Step 3:** 2,5-Dibromo-4-(4-chlorobenzyl)thiazole

[00601] To a mixture of 4-(4-chlorobenzyl)thiazol-2-amine (6.90 g, 30.7 mmol) in acetonitrile (367 mL) was added copper(II) bromide (10.3 grams, 46.0 mmol) and the resulting mixture was stirred at room temperature for 4 hours. Butyl nitrite (5.21 mL, 46.0 mmol) was added and the mixture was stirred at

room temperature for 30 minutes. The reaction was concentrated in vacuo and the residue was slurried in DCM (250 mL) for 30 minutes. The mixture was filtered through Celite and washed with DCM (50 mL). The filtrate was concentrated in vacuo and the residue was purified by silica gel chromatography (ethyl acetate/hexanes = 0/100→10/90) to give 8.47 grams of the title compound as an orange oil (75 % yield). LC/MS (FA) ES+ 368, 370. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30-7.18 (m, 4H), 4.03 (s, 2H).

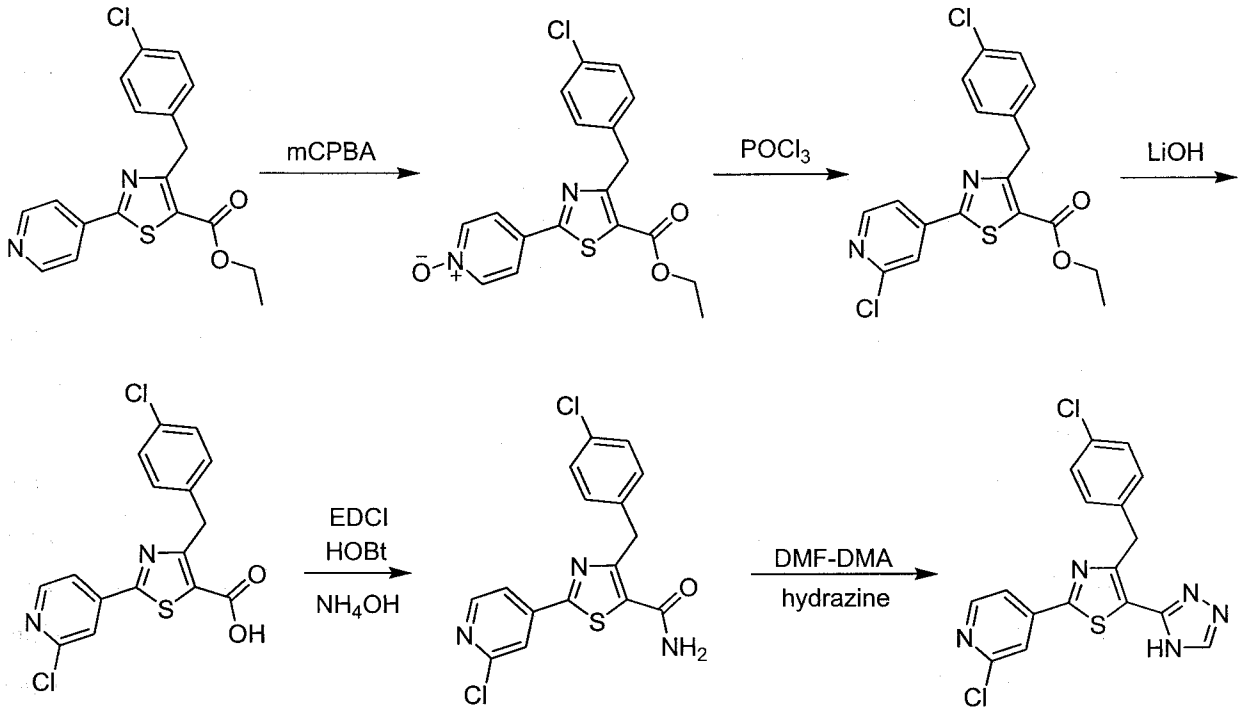
[00602] **Step 4:** 5-Bromo-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole

[00603] To a solution of 2,5-dibromo-4-(4-chlorobenzyl)thiazole (12.9 grams, 35.1 mmol) in DME (365 mL) was added pyridine-4-boronic acid (5.61 g, 45.6 mmol), 1M sodium carbonate (70.2 mL, 70.2 mmol), and $PdCl_2$(dppf) (2.89 g, 3.51 mmol). The reaction was degassed with argon and stirred at 85°C overnight. The reaction was cooled and taken up in ethyl acetate (400 mL) and saturated sodium bicarbonate (200 mL). The insolubles were filtered through celite and the bed was washed with ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→70/30) followed by another silica gel chromatography (ethyl acetate/hexanes = 0/100→100/0) to give 3.3 grams of the title compound as a brown solid (26% yield). LC/MS (FA) ES+ 365, 367. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.70-8.67 (m, 2H), 7.70-7.67 (m, 2H), 7.28-7.26 (m, 4H), 4.13 (s, 2H).

[00604] **Step 5:** 4-(4-Chlorobenzyl)-2-(pyridin-4-yl)-5-(1H-pyrrol-2-yl)thiazole (Compound **22**).

[00605] To a solution of 5-bromo-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole (94.0 mg, 0.257 mmol) in 4:1 dioxane:water (3.0 mL) was added 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (57 mg, 0.27 mmol), cesium carbonate (251 mg, 0.771 mmol), and tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.026 mmol). The solution was degassed with argon and heated in a microwave reactor at 130°C for 105 minutes. The reaction was concentrated in vacuo and the residue taken up in DCM (25 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→80/20) followed by HPLC purification (formic acid method) to give 26 mg of the title compound as a yellow solid (29 % yield). LC/MS (FA) ES+ 352. ^{1}H NMR (300 MHz, d_4-MeOH) δ: 8.62-8.60 (m, 2H), 7.90-7.88 (m, 2H), 7.66-7.55 (m, 1H), 7.26-7.24 (m, 2H), 7.20-7.17 (m, 2H), 6.92 (dd, 1H, J = 2.7, 1.5 Hz), 6.32 (dd, 1H, J = 3.5, 1.5 Hz), 6.21 (dd, 1H, J = 3.5, 2.7 Hz), 4.28 (s, 2H).

[00606] **Example 20: Synthesis of 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound 47)**



[00607] **Step 1:** 4-(4-(4-Chlorobenzyl)-5-(methoxycarbonyl)thiazol-2-yl)pyridine 1-oxide

[00608] To a solution of ethyl 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylate (430 mg, 1.20 mmol) in DMF (6.0 mL) was added mCPBA (322 mg, 1.44 mmol) and the mixture was stirred at room temperature overnight. To the reaction was added DCM (30 mL) and saturated sodium bicarbonate (25 mL). The layers were separated and the aqueous layer extracted with DCM (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 50/50→100/0) to give 449 mg of the title compound as a white solid (100 % yield). LC/MS (FA) ES+ 375. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23-8.20 (m, 2H), 7.84-7.81 (m, 2H), 7.33-7.23 (m, 4H), 4.51 (s, 2H), 4.38 (q, 2H, J = 7.2 Hz), 1.39 (t, 3H, J = 7.2 Hz).

[00609] **Step 2:** Ethyl 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxylate

[00610] A solution of 4-(4-(4-chlorobenzyl)-5-(methoxycarbonyl)thiazol-2-yl)pyridine 1-oxide (334 mg, 0.891 mmol) in phosphoryl chloride (1.66 mL, 17.8 mmol) was heated at 100°C for 2 hours. The reaction was cooled and poured onto ice and saturated sodium bicarbonate (50 mL). The mixture was extracted with ethyl acetate (2 x 40 mL) and the combined organic layers were washed with water (20 mL), brine (10 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (DCM/hexanes = 50/50→100/0) to give 191 mg of the title compound as a white solid (54 % yield). LC/MS (FA) ES+ 393, 395. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.49 (dd, 1H, J = 5.3, 0.7 Hz), 7.88 (dd, 1H, J = 1.5, 0.7 Hz), 7.71 (dd, 1H, J = 5.3, 1.5 Hz), 7.36-7.31 (m, 2H), 7.27-7.23 (m, 2H), 4.53 (s, 2H), 4.39 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz).

[00611] **Step 3:** 4-(4-Chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxylic acid

[00612] To a solution of ethyl 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxylate (199 mg, 0.506 mmol) in THF (2.84 mL) and water (1.42 mL) was added 1.0 M LiOH (0.658 mL, 0.658 mmol) and the resulting solution was stirred at room temperature overnight. The mixture was acidified to pH = 4 with 1 N HCl. The precipitated solids were filtered, washed with water and dried to give 179 mg of the title compound as an a white solid. (96 % yield). LC/MS (FA) ES+ 365, 367.

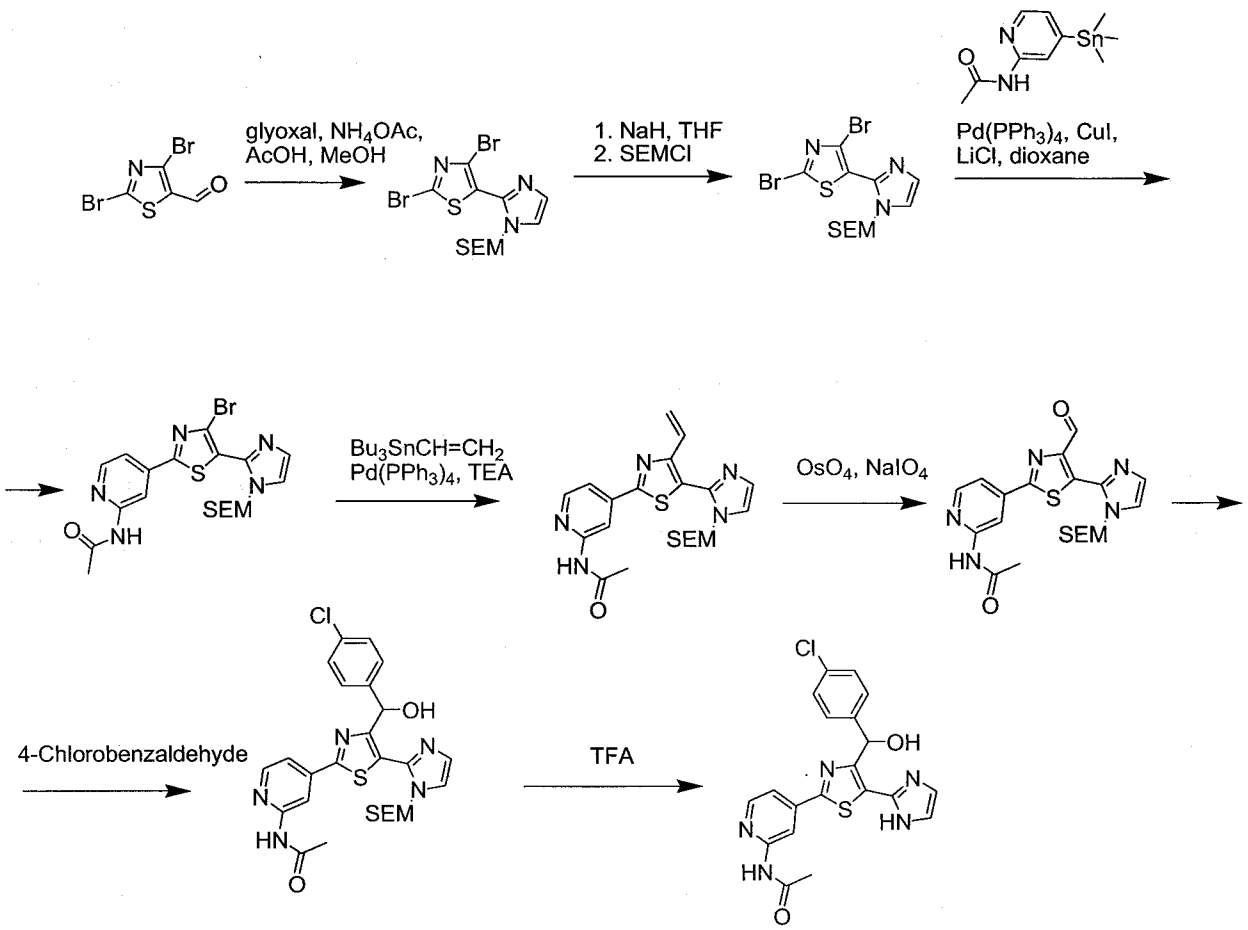
[00613] **Step 4**: 4-(4-Chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxamide

[00614] To a mixture of 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxylic acid (179 mg, 0.490 mmol) in DCM (27.5 mL) was added EDCI (282 mg, 1.47 mmol) and 1-hydroxybenzotriazole hydrate (150 mg, 0.980 mmol) and the solution was stirred for 10 minutes. 28% ammonium hydroxide (2.12 mL, 24.5 mmol) was added and the resulting mixture was stirred at room temperature overnight. Water (20 mL) was added and the mixture was extracted with DCM (2 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (methanol/DCM = 0/100→15/85) to give 121 mg of the title compound as a white solid (67 % yield). LC/MS (FA) ES+ 364, 366. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.54 (dd, 1H, J = 5.2, 0.7 Hz), 8.02 (bs, 1H), 7.91 (dd, 1H, J = 1.5, 0.7 Hz), 7.84 (dd, 1H, J = 5.2, 1.5 Hz), 7.79 (bs, 1H), 7.36-7.29 (m, 4H), 4.43 (s, 2H).

[00615] **Step 5:** 4-(4-Chlorobenzyl)-2-(2-chloropyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound **47**).

[00616] A solution of 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxamide (128 mg, 0.351 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (0.467 mL, 3.51 mmol) in toluene (3.75 mL) was heated at 100 °C for 1 hour. The reaction was cooled and concentrated in vacuo to give the intermediate, 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)-N-((dimethylamino)methylene)thiazole-5-carboxamide, as a solid. LC/MS (FA) ES+ 419, 421. The intermediate was dissolved in acetic acid (3.60 mL). Hydrazine hydrate (0.0855 mL, 1.76 mmol) was added and the resulting solution was heated at 90°C for 2 hours. The mixture was cooled and concentrated in vacuo, and the residue was azeotroped with toluene. The residue was slurried in DCM (30 mL) and saturated sodium bicarbonate (20 mL). Some undissolved solids were filtered to give one batch of desired product. The layers of the filtrate were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give another batch of desired product. The two product batches were combined and purified by silica gel chromatography (methanol/DCM = 0/100→20/80) to give 85 mg of the title compound as a beige solid (62 % yield). LC/MS (FA) ES+ 388, 390. ^{1}H NMR (300 MHz, d_6-DMSO) δ: 14.48 (bs, 1H), 8.76 (s, 1H), 8.54-8.51 (m, 1H), 7.96-7.95 (m, 1H), 7.92-7.89 (m, 1H), 7.38-7.30 (m, 4H), 4.65 (s, 2H).

[00617] Example 21: Synthesis of N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1H-imidazol-2-yl)-1,3-thiazol- 2-yl]pyridin-2-yl}acetamide (Compound 60)



[00618] Step 1: 2,4-Dibromo-5-(1H-imidazol-2-yl)thiazole

[00619] A mixture of 2,4-dibromo-thiazole-5-carbaldehyde (14.8 g, 54.6 mmol), glyoxal trimer dihydrate (22.96 g, 109.2 mmol) and ammonium acetate (25.26 g, 327.8 mmol) in MeOH (450 mL) and acetic acid (31.06 mL) was stirred at rt overnight. The reaction mixture was concentrated in vacuo to a thick liquid mixture. Remaining acetic acid was removed by azeotroping with toluene (3 x 100 mL) to afford a dark brown solid. The mixture was purified by column chromatography on silica gel (0 to 25% EtOAc in hexanes) to give pure product (9.12 g, 54%). LCMS: (AA) ES+, 310, 312. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 12.50 (br, 1H), 7.21 (br, 2H).

[00620] Step 2: 2,4-Dibromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazole

[00621] To a mixture of sodium hydride (2.89 g, 72.2 mmol) in THF (431 mL) was added 2,4-dibromo-5-(1H-imidazol-2-yl)thiazole (18.8 g, 60.9 mmol) in THF (60 mL) at 0 °C . After stirring 30

min, 2-(trimethylsilyl)ethoxymethyl chloride (11.8 mL, 66.9 mmol) in THF (24 mL) was slowly added at 0 °C . After 30min at this temperature, the reaction was quenched by the addition of MeOH (20 mL). The solvent was evaporated and the residue was purified by column chromatography on silica gel (0 to 25% EtOAc in hexanes). Product was obtained as colorless oil (21.8 g, 81.6%). LCMS: (AA) ES+, 440, 442. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 (dd, 2H), 5.27 (s, 2H), 3.39 (t, 2H), 0.85 (t, 2H), -0.03(s, 9H).

[00622] **Step 3:** N-(4-(4-Bromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazol-2-yl)pyridin-2-yl)acetamide

[00623] A mixture of 2,4-dibromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazole (13.6 g, 31.0 mmol), N-[4-(trimethylstannyl)pyridin-2-yl]acetamide (11.1 g, 37.2 mmol), tetrakis(triphenylphosphine)palladium(0) (1.792 g, 1.550 mmol), copper(I) iodide (1.77 g, 9.30 mmol) and lithium chloride (3.94 g, 93.0 mmol) in 1,4-dioxane (569 mL) was degassed with argon. The mixture was sonicated for 20min and then heated at 120°C for 5 h. The solvent was evaporated and the crude reaction mixture was purified by ISCO chromatography (0 to 3% MeOH in DCM). Product was obtained as an orange solid (10.1 g, 66.0%). LCMS: (AA) ES+, 494, 496. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.65 (s, 1H), 8.44 (br, 1H), 8.34 (d, 1H), 7.60 (dd, 1H), 7.30 (d, 2H), 5.30 (s, 2H), 3.40 (t, 2H), 2.25 (s, 3H), 0.86 (t, 2H), -0.05 (s, 9H).

[00624] **Step 4:** N-{4-[5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)-4-vinyl- 1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00625] N-(4-(4-bromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazol-2-yl)pyridin-2-yl)acetamide (0.80 g, 1.6 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.187 g, 0.162 mmol) were placed in a microwave vial and sealed under atmosphere of argon. Triethylamine (7.0 mL, 50 mM), THF (7 mL) and tributylethenyl stannane (0.708 mL, 2.43 mmol) were added and the mixture was irradiated at 95°C for 3 hours. The solvent was evaporated and the residue was purified using column chromatography on silica gel (0 to 60% EA in hexane) to give the title compound (0.65 g, 72%). LCMS: (FA) ES+, 442. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (s, 1H), 8.41-8.31 (m, 1H), 8.09 (s, 1H), 7.70-7.40 (m, 3H), 6.81 (dd, J = 17.2, 10.7 Hz, 1H), 6.38 (dd, J = 17.2, 1.9 Hz, 1H), 5.54 (dd, J = 10.7, 1.9 Hz, 1H), 5.27 (s, 2H), 3.48-3.34 (m, 2H), 2.25 (s, 3H), 0.90-0.84 (m, 2 H), -0.04 (s, 9 H).

[00626] **Step 5:** N-{4-[4-formyl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)- 1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00627] N-{4-[5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)-4-vinyl-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.650 g, 1.47 mmol) was dissolved in tetrahydrofuran (20 mL) and water (10 mL) at ambient temperature and 0.157 M osmium tetraoxide in water (93 uL, 0.014 mmol) was added. The mixture was stirred at room temperature for 5 minutes. Sodium metaperiodate (0.661 g, 3.09 mmol)

was then added in portions over 20 minutes and the mixture was stirred at room temperature overnight. Solids were removed by filtration and washed with THF (2 x 50 mL) and ethyl acetate (2 x 5 mL). The filtrate was extracted with ethyl acetate (3 x 100 mL). The extracts were combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Crude material was purified by silica gel chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (0.25 g, 38%). LCMS: (FA) ES+, 444. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (s, 1H), 10.21 (s, 1H), 8.41 (d, J = 5.18 Hz, 1H), 8.20-8.07 (m, 1H), 7.76 (dd, J = 5.21, 1.58 Hz, 1H), 7.30 (dd, J = 2.87, 1.21 Hz, 2H), 5.32 (s, 2H), 3.50-3.33 (m, 2H), 2.26 (s, 3H), 0.93-0.78 (m, 2H), -0.04 (s, 9H).

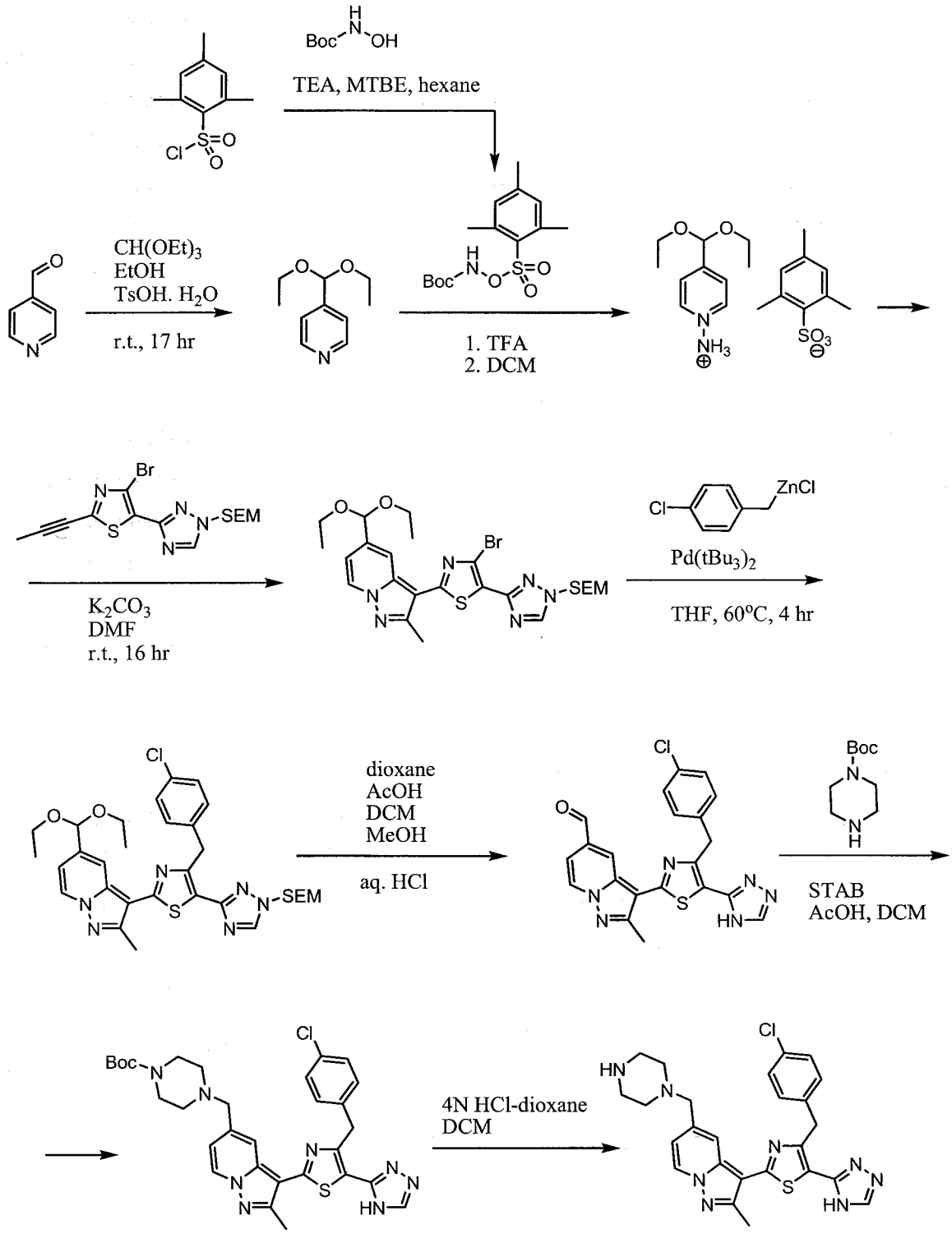
[00628] **Step 6:** N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00629] N-{4-[4-formyl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.250 g, 0.564 mmol) was dissolved in tetrahydrofuran (20 mL) and cooled at 0°C. 1.0 M 4-Chlorophenylmagnesium bromide in ether (1.41 mL, 1.41 mmol) was added and the solution was stirred at 0°C for 30 minutes. The reaction was quenched by the addition of MeOH (10 mL), and was evaporated under reduced pressure. The residue was purified using column chromatography (20 to 100% ethyl acetate in hexane) to give the title compound (0.150 g, 48%). LCMS: (FA) ES+, 556, 558. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (s, 1H), 8.34 (d, J = 5.23 Hz, 1H), 8.21 (s, 1H), 7.65 (dd, J = 5.23, 1.55 Hz, 1H), 7.31 (d, J = 8.28 Hz, 2H), 7.21-7.16 (m, 3H), 7.07 (d, J = 1.31 Hz, 1H), 6.26-6.15 (m, 1H), 5.30 (s, 1H), 3.46-3.36 (m, 2H), 2.24 (s, 3H), 0.94-0.84 (m, 2H), -0.02 (s, 9H).

[00630] **Step 7:** N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1H-imidazol-2-yl)-1,3-thiazol- 2-yl]pyridin-2-yl}acetamide (Compound 60)

[00631] N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.120 g, 0.216 mmol) was dissolved in DCM (5 mL) and trifluoroacetic acid (5.0 mL, 65 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated, azeotroped with toluene and purified using column chromatography on silica gel (0 to 10% MeOH in DCM) to give the title compound (0.050 g, 50%). LCMS: (FA) ES+, 426, 428. ^{1}H NMR (400 MHz, d_4-methanol) δ: 8.68 (s, 1H), 8.38 (d, J = 5.24 Hz, 1H), 7.64 (dd, J = 5.25, 1.60 Hz, 1H), 7.45-7.37 (m, 2H), 7.30-7.23 (m, 2H), 7.25-7.09 (m, 2H), 6.37 (s, 1H), 2.20 (s, 3H).

[00632] **Example 22: Synthesis of 3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methyl-5-(piperazin-1-ylmethyl)pyrazolo[1,5-a]pyridine (Compound 72)**



[00633] **Step 1:** 4-(Diethoxymethyl)pyridine:

[00634] p-Toluenesulfonic acid monohydrate (11.8 g, 62.0 mmol) was dissolved in dry ethanol (80 mL) at rt. 4-Pyridinecarboxaldehyde (4.71 mL, 50.0 mmol) was added, followed by ethyl orthoformate

(20.79 mL, 125.0 mmol). The mixture was stirred at rt for 17 hours. The mixture was concentrated and the residue was basified with aqueous saturated $NaHCO_3$ solution to ~pH 8, extracted with EtOAc (150 mL), washed with brine, dried over Na_2SO_4, filtered, evaporated, and dried under high vacuum to give a liquid product. (9.06 g, yield 97.2%). LCMS: (FA) ES^+ 182. ^1H NMR (400MHz, $CDCl_3$) δ: 8.60-8.62 (m, 2H), 7.38-7.40 (m, 2H), 5.50 (s, 1H), 3.53-3.62 (m, 4H), 1.23-1.27 (m, 6H).

[00635] **Step 1A:** N-tert-Butoxycarbonyl-O-(mesitylsulfonyl)hydroxylamine

[00636] tert-Butyl-N-hydroxycarbamate (5.00 g, 37.6 mmol) and mesitylenesulfonyl chloride (8.21 g, 37.6 mmol) were dissolved in 2-methoxy-2-methylpropane (90 mL), flushed with nitrogen and cooled in an ice bath to an internal temperature of 1°C. Triethylamine (5.34 mL, 38.3 mmol) was added dropwise over 25 min during which time the temperature increased to 6°C. The mixture was stirred with cooling for 2 hours at which time the internal reaction temperature was 8°C. The suspension was filtered and the solids were washed with 2-methoxy-2-methylpropane (60 mL). The filtrate was concentrated to ~20 mL volume, diluted with hexane (70 mL) and allowed to sit at rt for 30 min. The resulting crystalline solid was collected by filtration and washed with hexane (20 mL). The mother liquor was evaporated, diluted with hexane (50 mL), and allowed to sit, giving a second crop of crystals. The combined collected solids were dried in vacuum for 1 hour to give a white crystal product (11.06g, yield 93.4%). LCMS: (AA) ES^+ 316 and 333 for M^++NH_3. ^1H NMR (400MHz, $CDCl_3$) δ: 7.54 (s, 1H), 6.99 (s, 2H), 2.68 (s, 6H), 2.32 (s, 3H), 1.31 (s, 9H).

[00637] **Step 2:** 1-Amino-4-(diethoxymethyl)pyridinium 2,4,6-trimethylbenzenesulfonate

[00638] Trifluoroacetic acid (12.0 mL, 156 mmol) was cooled in an ice bath. N-tert butoxycarbonyl-O-(mesitylsulfonyl)hydroxylamine (7.91 g, 25.1 mmol) was portionwise added over 15 min. The mixture was stirred with cooling for 2 hours then ~50 g of ice was added, followed by ~100 mL of ice water. The resulting white solid was collected by filtration and washed with water until the washings were ~pH 6. The solid was dried in air for 15 min to afford a still damp intermediate (6.25 g). The solid then was dissolved in methylene chloride (160 mL, 2500 mmol), dried over Na_2SO_4, and filtered. The filtrate was cooled in an ice bath and a solution of 4-(diethoxymethyl)pyridine (5.91 g, 32.6 mmol) in dry methylene chloride (20 mL, 300 mmol) was slowly added over 10 min. The ice bath was removed and the mixture was stirred at rt for 50 min. The mixture was concentrated to ~30 mL volume. The oily residue was azeotroped with 15 mL of diethyl ether, then the residue was diluted with 250 mL of diethyl ether and cooled in an ice bath for 1 hour, then stored in a freezer (-20°C) overnight. An oily residue appeared. The clear solution was decanted and the oily residue was dried under high vacuum to give a first crop of oily product (2.15g). The decanted solution was concentrated to give an oily residue which was triturated with hexane (2 x 100 mL), then dried under high vacuum to give a second crop of oily product (6.15g, yield 79.7% for 2 crops). LCMS: (FA) ES^+ 197; ES^- 199. ^1H NMR (400MHz, $CDCl_3$) δ: 9.00-9.05 (m, 4H),

7.69-7.71 (m, 2H),6.85 (s, 2H), 5.50 (s, 1H), 3.52-3.57 (m, 4H), 2.67 (s, 6H), 2.25 (s, 3H), 1.22-1.26 (m, 6H).

[00639] **Step 3:** 3-[4-Bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-5-(diethoxymethyl)-2-methylpyrazolo[1,5-a]pyridine

[00640] To a mixture of 3-(4-bromo-2-prop-1-yn-1-yl-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole [Prepared as described in Example 14 (4.37 g, 10.9 mmol)] and potassium carbonate (3.00 g, 21.7 mmol) in dry N,N-dimethylformamide (20.0 mL) was added a solution of 1-amino-4-(diethoxymethyl)pyridinium 2,4,6-trimethylbenzenesulfonate (6.37 g, 15.6 mmol) in dry N,N-dimethylformamide (20.0 mL) over 10 min. The resulting dark brown solution was stirred at rt for 40 hours. The mixture was added to ~250 mL of ice water with stirring, then was extracted with EtOAc (100 mL x 5) until the aqueous layer turned into a clear solution. The combined EtOAc extracts were washed with water, brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography on silica gel, using EtOAc/hexane (0/100 to 50/50) as an eluant to give a solid product (4.56g, 70.2%). LCMS: (FA) ES^+ 593, 595. ^1H NMR (400MHz, $CDCl_3$) δ: 8.46 (d, J = 2.01 Hz, 1H), 8.40-8.42 (d, J = 7.28 Hz, 1H), 8.32 (s, 2H), 7.05-7.08 (dd, J = 2.01, 7.03 Hz, 1H),5.57(s, 2H)3.68-3.77 (m, 4H), 3.58-3.63 (m, 2H), 2.75 (s, 3H), 1.28-1.32 (m, 6H), 0.95-1.00 (m, 2H),0.02 (s, 9H)

[00641] **Step 4:** 3-[4-(4-Chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-5-(diethoxymethyl)-2-methylpyrazolo[1,5-a]pyridine

[00642] A mixture of 3-[4-bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-5-(diethoxymethyl)-2-methylpyrazolo[1,5-a]pyridine (0.907 g, 1.53 mmol) and bis(tri-t-butylphosphine)palladium(0) (39.0 mg, 0.0764 mmol) in a 40 mL vial was evacuated under low vacuum and backfilled with nitrogen four times. 4-Chlorobenzylzinc chloride in tetrahydrofuran (0.50 M, 7.0 mL, 3.5 mmol) was added and the solution was again evacuated under low vacuum and backfilled with nitrogen twice. The solution was heated to 60°C for 4 hours. The reaction mixture was cooled to rt, quenched with water, adjusted to ~ pH 6 with acetic acid, and extracted with EtOAc (2x). The organic layers were combined, washed with water, brine, dried over Na_2SO_4, filtered and evaporated to give a crude residue which was purified by column chromatography on silica gel column using EtOAc/hexane (0/100 to 40/60) as an eluant to give a solid product (0.806g, 85% pure by 1H-NMR, yield 70.5%). LCMS: (FA) ES^+ 639, 641. ^1H NMR of pure fraction (400MHz, $CDCl_3$) δ: 8.36-8.39 (m, 2H), 8.27 (s, 1H), 7.45-7.47 (m, 2H), 7.23-7.25 (m, 2H), 6.99-7.01 (m, 1H),5.54 (s, 2H, 5.50 (s, 1H), 4.67 (s, 2H), 3.66-3.74 (m, 4H), 3.57-3.62 (m, 2H), 2.74 (s, 3H), 1.26-1.30 (m, 6H), 0.95-0.99 (m, 2H),0.00 (s, 9H).

[00643] **Step 5:** 3-[4-(4-Chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridine-5-carbaldehyde

[00644] 3-[4-(4-Chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-5-(diethoxymethyl)-2-methylpyrazolo[1,5-a]pyridine (1.17 g, 1.83 mmol) was dissolved in 1,4-dioxane (45 mL) and cooled in a water bath. 12 M hydrochloric acid (15 mL) was added and the mixture was stirred at rt for 15 hours. Acetic acid (40 mL, 700 mmol) was added and the suspension was stirred at rt for 24 hours then heated to 70° C for 2 hours, then evaporated. The solid residue was stirred with 1.00 hydrochloric acid (100 mL) and methanol (120 mL) at rt for 14 hours. The mixture was evaporated on a rotovap at 45°C to dryness and then azeotroped with DCM to give a crude product. The crude product was suspended in water, basified with $NaHCO_3$ to ~pH 8, extracted with EtOAc (300 mL, 3 x 80 mL), washed with brine, dried over Na_2SO_4, filtered, and evaporated to afford a yellow solid product (0.773 g, yield 97.2%). LCMS: (FA) ES^+ 435, 437. ^1H NMR (400MHz, $CDCl_3$) δ: 10.84 (s, br, 1H), 9.99 (s, 1H), 8.75 (m, 1H), 8.43-8.46 (d, J = 7.28 Hz, 1H), 8.36 (s, 1H), 7.41-7.44 (d, J = 8.53 Hz, 2H), 7.32-7.35 (dd, J = 7.03, 2.01 Hz, 1H), 7.27-7.30 (d, J = 8.53 Hz, 2H), 4.69 (s, 2H), 2.79 (s, 3H).

[00645] **Step 6:** tert-Butyl 4-({3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methyl)piperazine-1-carboxylate

[00646] A mixture of 3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridine-5-carbaldehyde (0.0563 g, 0.109 mmol), tert-butyl 1-piperazinecarboxylate (60.8 mg, 0.326 mmol) and acetic acid (0.0800 mL, 1.41 mmol)in dry methylene chloride (10 mL) was stirred at rt for 15 min. Sodium triacetoxyborohydride (69.1 mg, 0.326 mmol) was added and the mixture was stirred at rt for 15 hours. The mixture was washed with saturated $NaHCO_3$ solution and the aqueous layer was extracted with DCM. The DCM extract was washed with water, brine, dried over Na_2SO_4, filtered and evaporated to give a crude product which was purified by column chromatography on silica gel column using MeOH/DCM (0/100 to 5/95) to give solid product (0.0464g, yield 70.5%). LCMS: (FA) ES^+ 605, 607; ES^- 603, 605. ^1H NMR (400MHz, $CDCl_3$ and d_4-methanol) δ: 8.23-8.25 (d, J = 7.03 Hz, 1H), 8.20 (s, 1H), 7.94 (s, 1H), 7.29-7.31 (d, J = 8.28 Hz, 2H), 7.15-7.17 (d, J = 8.53 Hz, 2H), 6.86-6.89 (dd, J = 7.28, 1.76 Hz, 1H), 4.53 (s, 2H), 3.45 (s, 2H), 3.33-3.36 (m, 4H), 2.62 (s, 3H), 2.35 (s, br, 4H), 1.37 (s, 9H).

[00647] **Step 7:** 3-[4-(4-Chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methyl-5-(piperazin-1-ylmethyl)pyrazolo[1,5-a]pyridine (Compound **72**)

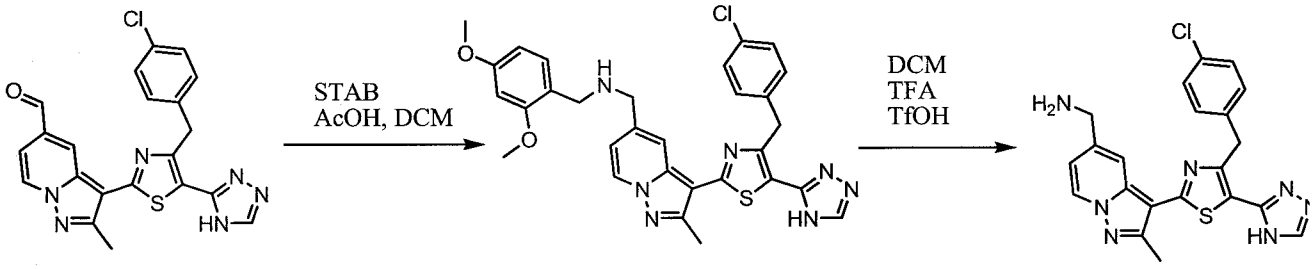
[00648] To a solution of tert-butyl 4-({3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methyl)piperazine-1-carboxylate (0.0435 g, 0.0719 mmol) in methylene chloride (2.0 mL) and methanol (2.0 mL) was added 4 M hydrochloric acid in 1,4-dioxane (2.0 mL, 7.8 mmol). The mixture was stirred at rt for 5 hours then was evaporated, azeotroped with MeOH, and dried under high vacuum to give a solid (~50 mg). The solid was triturated with diethyl ether (10 ml x 2) then dried under high vacuum to give product as a pale yellow powder (0.0424g, yield 100%) as a bis

HCl salt. LCMS: (FA) ES^+ 505, 507; ES^- 503, 505. ^1H NMR (400MHz, d_4-methanol) δ: 8.71 (s, 1H), 8.62-8.64 (d, J = 7.03 Hz, 1H), 8.41 (s, 1H), 7.39-7.41 (d, J = 8.78 Hz, 2H), 7.27-7.29 (d, J = 8.53 Hz, 2H), 7.20-7.23 (dd, J = 7.03, 2.01 Hz, 1H), 4.66 (s, 2H), 4.38 (s, 2H), 3.54 (s, br, 4H), 3.43 (s, br, 4H), 2.73 (s, 3H).

[00649] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 22:

31	LCMS: (FA) ES+ 570, 572.
32	LCMS: (FA) ES+ 526, 528.
38	LCMS: (FA) ES+ 493, 495.
54	LCMS: (FA) ES+ 479, 481.
61	LCMS: (FA) ES+ 519, 521.
82	LCMS: (FA) ES+ 579, 581.
83	LCMS: (FA) ES+ 569, 571.

[00650] **Example 23: Synthesis of 1-{3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methanamine (Compound 1)**



[00651] **Step 1:** 1-{3-[4-(4-Chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}-N-(2,4-dimethoxybenzyl)methanamine

[00652] To a suspension of 3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridine-5-carbaldehyde (0.300 g, 0.690 mmol) in acetic acid (0.20 mL, 3.5 mmol) and dry methylene chloride (10 mL, 200 mmol) was added 2,4-dimethoxybenzylamine (0.207 mL, 1.38 mmol), followed by additional of sodium triacetoxyborohydride (0.363 g, 1.71 mmol). The mixture was stirred at rt. for 16 hours. The mixture was basified with $NaHCO_3$ solution to ~pH 8 then extracted with DCM. The DCM solution was washed with water. The crude product was purified by column chromatography (SiO2, elution with 0-100% MeOH in DCM) to afford a solid product (0.252 g, yield

62%). LCMS: (FA) ES^+ 586, 588; ES^- 584, 586. ^1H NMR (400MHz, $CDCl_3$ and d_4-methanol) δ: 8.23-8.25 (d, J = 7.03 Hz, 1H), 8.18 (s, 1H), 8.01 (s, 1H), 7.28-7.30 (d, J = 8.53 Hz, 2H), 7.09-7.11 (d, J = 8.53 Hz, 2H), 7.01-7.03 (d, J = 8.28 Hz, 1H), 6.78-6.80 (d, J = 7.03 Hz, 1H), 6.33-6.37 (m, 2H), 4.53 (s, 2H), 3.65 (s, 2H), 3.64 (s, 6H), 3.61 (s, 2H), 2.61 (s, 3H).

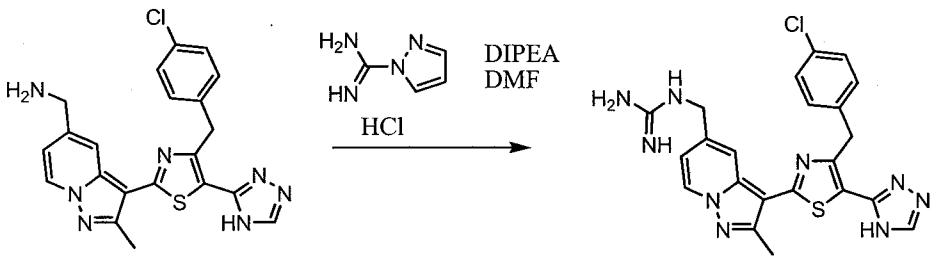
[00653] **Step 2:** 1-{3-[4-(4-Chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methanamine (Compound **1**)

[00654] 1-{3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}-N-(2,4-dimethoxybenzyl)methanamine (0.257 g, 0.438 mmol) was dissolved in methylene chloride (6.0 mL) and trifluoroacetic acid (6.0 mL). Trifluoromethanesulfonic acid (0.050 mL, 0.56 mmol) was added and the mixture was heated to 60°C for 6 days. The mixture was evaporated in a rotary evaporator, azeotroped with EtOAc (3 x), and evaporated to give a crude residue. The residue was suspended in ~1 mL of MeOH and diluted with ~20 mL of Et_2O. The resulting powder was collected by filtration and dried under high vacuum to afford a pale pink solid product. The solid was taken up in EtOAc / water (20 mL / 10 mL) and adjusted to ~pH 8 with $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with EtOAc (2x30 mL). The combined EtOAc solutions were washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to ~5 mL volume and the precipitated solid was collected by filtration to give a pure crop of product (0.0069 g). The filtrate was evaporated then dried under high vacuum to afford a second crop of solid product (0.171g, yield for 2 crops 89.9%). LCMS: (FA) ES^+ 436, 438; ES^- 434, 436. ^1H NMR (400MHz, d_4-methanol) δ: 8.33-8.35 (d, J = 7.29 Hz, 1H), 8.24 (s, 1H), 8.09 (s, 1H), 7.31-7.33 (d, J = 8.78 Hz, 2H), 7.20-7.22 (d, J = 8.53 Hz, 2H), 6.98-7.00 (m, 1H), 4.59 (s, 2H), 4.06 (s, 2H), 2.67 (s, 3H).

[00655] Compound in the following table was prepared from the appropriate starting materials in a method analogous to that of Example 23:

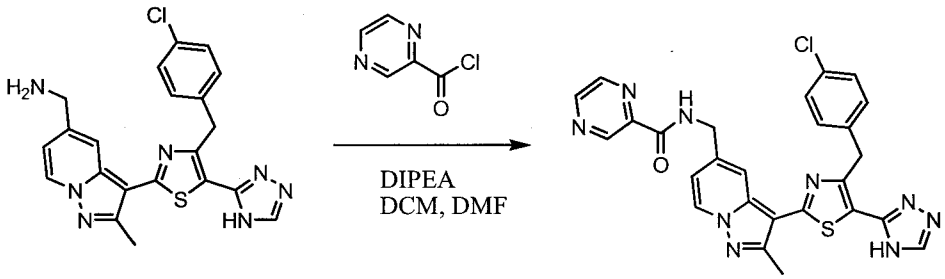
20	LCMS: (FA) ES+ 586, 588.

[00656] **Example 24: Synthesis of N-({3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methyl)guanidine (Compound 35)**



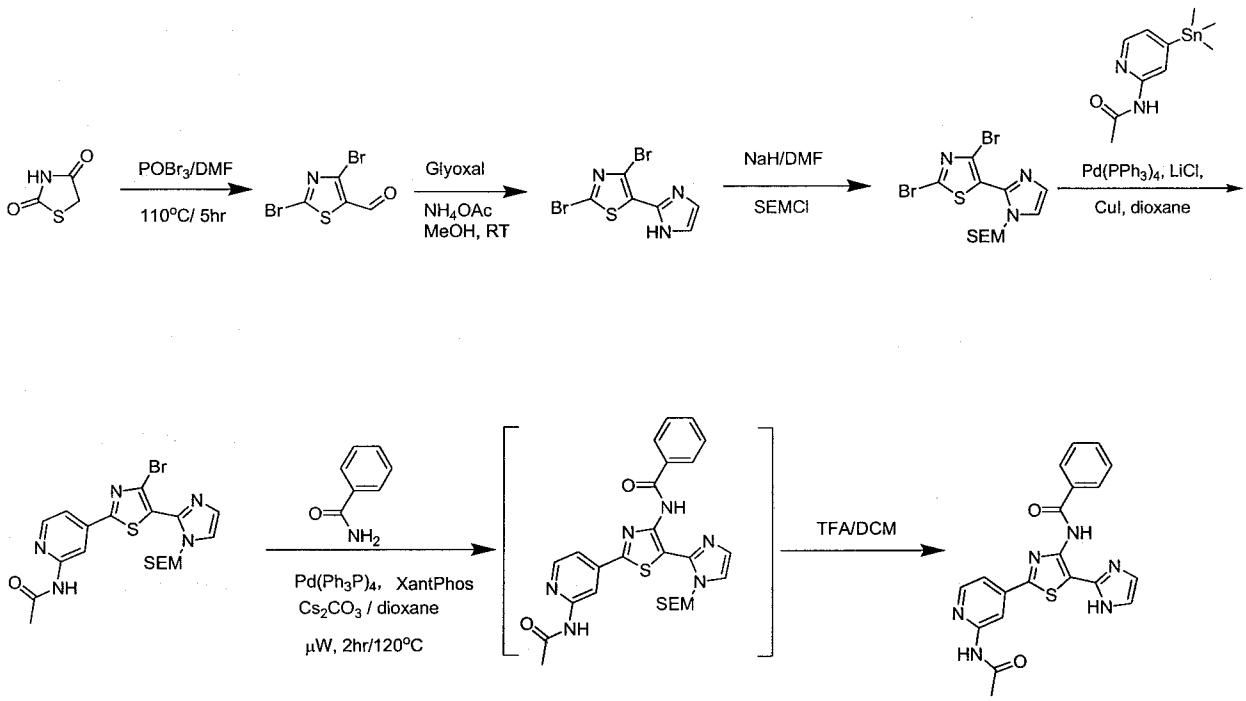
[00657] To a mixture of 1-{3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methanamine (0.0250 g, 0.0553 mmol) and 1H-pyrazole-1-carboxamidine hydrochloride (8.20 mg, 0.0559 mmol) in dry N,N-dimethylformamide (0.50 mL) was added N,N-diisopropylethylamine (7.15 mg, 0.0553 mmol). The solution was stirred at rt for 23 hours. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (5 x 15 mL). The EtOAc solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated in a rotary evaporator to give a crude residue. The residue was dissolved in ~0.2 mL of MeOH, then diluted with ~5 mL of EtOAc. The resulting solid was collected by filtration to give a pale yellow powder product (0.008 g, 30%). LCMS: (FA) ES^+ 478, 480; ES^- 476, 478. ^1H NMR (400MHz, $CDCl_3$ and d_4-methanol) δ: 8.25-8.27 (d, J = 7.28 Hz, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.21-7.23 (d, J = 8.53 Hz, 2H), 7.08-7.10 (d, J = 8.28 Hz, 2H), 6.72-6.74 (dd, J = 7.28, 1.76 Hz, 1H), 4.48 (s, 2H), 4.30 (s, 2H), 2.57 (s, 3H).

[00658] Example 25: Synthesis of N-({3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methyl)pyrazine-2-carboxamide (Compound 50)



[00659] A mixture of 1-{3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methanamine (0.0222 g, 0.0491), pyrazine-2-carboxylic acid chloride (8.0 mg, 0.056 mmol) and N,N-diisopropylethylamine (10 mg, 0.08 mmol) in dry Methylene chloride (5.0 mL) in dry N,N-dimethylformamide (1.0 mL) was sonicated for 2 min. The mixture was stirred at rt for 22 hours. N,N-diisopropylethylamine (13 mg, 0.10 mmol) and pyrazine-2-carboxylic acid chloride (9.11 mg, 0.0639 mmol) were added and the mixture was stirred at rt for 3 days. The mixture was quenched with water, then extracted with DCM (3 x 30 mL). The combined DCM solutions were washed with water, brine, dried over Na_2SO_4, filtered, and evaporated to give a crude product (80 mg). The crude product was purified by HPLC to give a solid product (0.0007 g, yield 3%). LCMS: (AA) ES^+ 542, 544. ^1H NMR (400MHz, d_6-DMSO) δ: 9.72-9.74 (d, J = 6.53 Hz, 1H), 9.23 (s, 1H), 8.87 (s, 1H), 8.75 (s, 1H), 8.67-8.69 (d, J = 6.53 Hz, 1H), 8.63 (s, 1H), 8.22 (s, 1H), 7.24-7.30 (m, 4H), 7.03-7.05 (d, J = 7.28 Hz, 1H), 4.62-4.64 (d, J = 6.78 Hz, 2H), 4.47 (s, 2H), 2.63 (s, 3H).

[00660] Example 26: Synthesis of N-(2-(2-acetamidopyridin-4-yl)-5-(1H-imidazol-2-yl)thiazol-4-yl)benzamide (Compound 29)



[00661] **Step 1:** 2,4-Dibromo-thiazole-5-carbaldehyde

[00662] 2,4-Thiazolidinedione (3.50 g, 0.0299 mol) and phosphorus oxybromide (42.76 g, 0.1491 mol) were placed into a two-neck round bottomed flask and the solid mixture was well mixed. The flask was evacuated and filled with argon. N,N-dimethylformamide (2.54 mL, 0.0329 mol) was added via syringe with hand shaking of the flask at the sametime. The mixture was stirred at rt for 2 hours and then heated slowly to 105°C, until the evolution of hydrogen bromide had ceased, (approximately 4h). The reaction was cooled to rt then the mixture was transferred to a beaker containg 200g of ice. The aqueous mixture was stirred with DCM then filtered. The DCM phase was separated and the aqueous phase was extracted with DCM twice. THe DCM layers were combined and washed with saturated sodium bicarbonate solution, then brine, dried over anhydrous sodium sulfate, filtered and concentrated. The mixture was dry loaded on silica gel and purified by chromatography to afford 2,4-dibromo-thiazole-5-carbaldehyde (2.50g, 30.9%). LCMS (FA) ES+ 272, 274.

[00663] **Step 2:** 2,4-Dibromo-5-(1H-imidazol-2-yl)thiazole

[00664] 2,4-Dibromo-thiazole-5-carbaldehyde (14.8 g, 54.6 mmol), hexahydro-[1,4]dioxino[2,3-b][1,4]dioxine-2,3,6,7-tetraol (22.96 g, 109.2 mmol), and ammonium acetate (25.26 g, 327.8 mmol) were added to a round bottomed flask followed by methanol (450 mL, 11000 mmol). The mixture was stirred and acetic acid (31.06 mL, 546.3 mmol) was added. The reaction was stirred overnight then the reaction mixture was concentrated under vaccuum to provide a thick liquid mixture. Toluene (100mL) was then added and reevaporated and this process was repeated several times to give a dark brown solid. Methanol

was added and the mixture was loaded on silica gel. Purification by column chromatography on silica gel afforded 2,4-dibromo-5-(1H-imidazol-2-yl)thiazole (9.12g, 54%). LCMS (AA) ES+ 310, 312, 308.

[00665] **Step 3:** 2,4-Dibromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazole

[00666] To a mixture of sodium hydride (2.89 g, 72.2 mmol) in tetrahydrofuran (431 mL, 5310 mmol) was added 2,4-dibromo-5-(1H-imidazol-2-yl)thiazole (18.81 g, 60.88 mmol) in tetrahydrofuran (60 mL, 700 mmol) at 0°C . The mixture was stirred for 30 min before [β-(Trimethylsilyl)ethoxy]methyl chloride (11.85 mL, 66.96 mmol) in tetrahydrofuran (24 mL, 3.0E2 mmol) was added slowly at 0°C . The reaction was quenched with MeOH. The solvent was evaporated and the residue was purified by column chromatography on silica gel to afford 2,4-dibromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazole (13.6g, 81.7%). LCMS (AA) ES+ 440, 442.

[00667] **Step 4:** N-(4-(4-bromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazol- 2-yl)pyridin-2-yl)acetamide

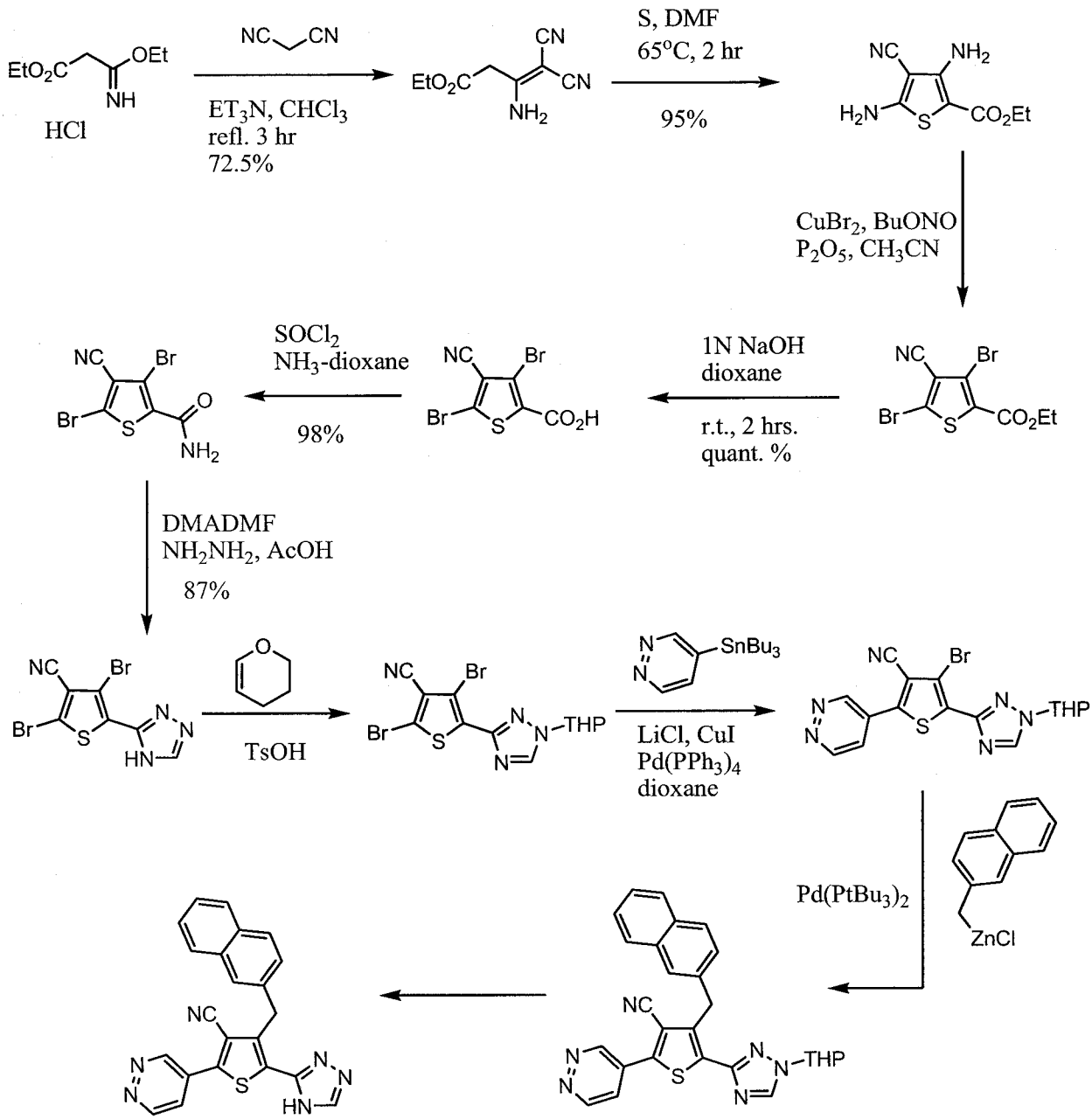
[00668] A mixture of 2,4-dibromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazole (13.62 g, 31.01 mmol), N-[4-(trimethylstannyl)pyridin-2-yl]acetamide (11.1 g, 37.2 mmol), tetrakis(triphenylphosphine)palladium(0) (1.792 g, 1.550 mmol), copper(I) iodide (1.772 g, 9.302 mmol) and lithium chloride (3.944 g, 93.02 mmol) in 1,4-dioxane (569 mL, 7290 mmol) was degassed and filled with argon three times. The mixture was sonicated for 20min and then heated at 120°C for 5h. The reaction mixture was dry loaded onto a silica gel column and purified by chromatography to afford N-(4-(4-bromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazol- 2-yl)pyridin-2-yl)acetamide as an orange solid. LCMS (AA) ES+ 494, 496.

[00669] **Step 5:** N-(2-(2-acetamidopyridin-4-yl)-5-(1H-imidazol-2-yl)thiazol-4-yl)benzamide (Compound **29**).

[00670] A mixture of N-(4-(4-bromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazol-2-yl)pyridin-2-yl)acetamide (80.9 mg, 0.164 mmol), benzamide (99.1 mg, 0.818 mmol), tris(dibenzylideneacetone)dipalladium(0) (21.3 mg, 0.0233 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (39.9 mg, 0.0690 mmol) and cesium carbonate (303 mg, 0.930 mmol) in 1,4-dioxane (7.66 mL, 98.2 mmol) was evacuated then filled with argon and then irradiated in microwave at 130°C for 3h. The reaction mixture was filtered and the filtrate was purified by column chromatography to afford the desired intermediate. LCMS (AA) ES+ 535, 536. To the above intermediate were added methylene chloride (1.2 mL, 19 mmol) and trifluoroacetic acid (1.8 mL, 23 mmol). The mixture was stirred at rt for 2h. The excess trifluoroacetic acid and solvent was evaporated and the residue was purified by HPLC to afford N-(2-(2-acetamidopyridin-4-yl)-5-(1H-imidazol-2-yl)thiazol-4-yl)benzamide (11.3mg, 17.1%). LCMS (FA) ES+ 406, 407; ^{1}H NMR (300 MHz, d_4-methanol) δ: 8.67 (d, J = 0.45 Hz, 1H), 8.40 (d, J =

5.23 Hz, 1H), 8.17-8.07 (m, 2H), 7.84-7.78 (m, 1H), 7.59 (dd, J = 13.90, 7.27 Hz, 3H), 7.22 (s, 2H), 2.22 (s, 3H).

[00671] Example 27: Synthesis of 4-(2-naphthylmethyl)-2-pyridazin-4-yl-5-(4H-1,2,4-triazol-3-yl)thiophene-3-carbonitrile (Compound 88)



[00672] Step 1: Ethyl 3-amino-4,4-dicyano-3-butenoate

[00673] Ethyl 3-ethoxy-3-iminopropionate hydrochloride (166 g, 721 mmol.) was suspended in dry methylene chloride (400 mL, 6000 mmol). Malononitrile (46.7 g, 707 mmol) was added, followed by

Triethylamine (1.00 mL, 721 mmol). The mixture was heated to reflux for 3 hours. The mixture was cooled to rt then quenched with 200 mL of water. The separated organic layer was washed with 2x200 mL of water. The combined aqueous layers were extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was further azeotroped with MTBE (2x200 mL) and ethyl acetate (70 mL). The residue was diluted with 70 mL of EtOAc. A precipitate appeared and the solid was collected by filtration and washed with ~20 mL of EtOAc until the pink-red color of the solid faded to give a first crop of product (32 g). The filtrate was concentrated in rotary evaporator and dried under high vacuum to a weight of ~110 g. More precipitate appeared after the concentrated filtrate sat for 1 hour. Approximately 50 mL of Et_2O was added and the mixture was allowed to sit overnight. The resulting precipitate was collected by filtration and washed with Et_2O to afford a second crop of solid product (20.59 g). The filtrate was concentrated in a rotary evaporator to give an oily residue. Chromatography on a silica column using EtOAc/hexane (short gradient from 0/100 to 50/50 then stayed on 50/50 for 100 min, with 120 mL/min flow rate) afforded a third crop of pure product (39.3 g, yield for all crops was 72.5%). LCMS: (FA) ES- 178. ^{1}H NMR (400MHz, $CDCl_3$) δ: 7.57 (s, br, 1H), 6.33 (s, br, 1H),4.24-4.30 (q, 2H), 3.63 (s, 2H), 1.31-1.35 (t, 3H).

[00674] **Step 2:** Ethyl 3,5-diamino-4-cyanothiophene-2-carboxylate

[00675] The mixture of ethyl 3-amino-4,4-dicyano-3-butenoate (91.9 g, 513 mmol) and sulfur (16.4 g, 513 mmol) in dry N,N-dimethylformamide (200 mL, 3000 mmol) was coooled in a water bath. Diethylamine (106 mL, 1020 mmol) was slowly added during which time the internal reaction temperature increased to 43°C. The dark-brown solution was then cooled in ice bath to rt (22°C) then the ice bath was removed. The mixture was stirred at rt for 3 hours. The mixture was poured into ice water (~1.4 L) and the resulting suspension was allowed to sit overnight.. The solid was collected by filtration and washed with 200 mL of water thoroughly to give a wet solid. The solid was stirred with 1.5 L of EtOAc at rt overnight, then filtered. The filtrate (EtOAc-water bilayer) was separated. The solid cake was dissolved in 1.2 L of EtOAc. The combined EtOAc solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, rotavaped and dried under high-vacuum overnight to give a dry powder product (102.6 g, yield 94.7%). LCMS: (FA) ES+ 212, ES- 210. ^{1}H NMR (400MHz, $CDCl_3$ and *d4*-methanol) δ: 4.14 (m, 2H), 1.21-1.25 (t, 3H).

[00676] **Step 3:** Ethyl 3,5-dibromo-4-cyanothiophene-2-carboxylate

[00677] Ethyl 3,5-diamino-4-cyanothiophene-2-carboxylate (25.0 g, 118 mmol) was dissolved in acetonitrile (500 mL, 10000 mmol). Copper(II) Bromide (105.7 g, 473.4 mmol) was added, followed by phosphorus pentoxide (6.72 g, 23.7 mmol). The mixture was stired at room temperature for 30 min, then cooled to 0°C. Butyl nitrite (56.4 mL, 473.4 mmol) was slowly added. After the completion of the

addition the mixture was heated to reflux for 1 h then cooled to room temperature. The reaction mixture was poured into 500 mL 4N HCl solution, then extracted with 500 mL DCM twice. The insoluble material was filtered off from the organic layer. The organic filtrate was dried over MgSO4, and filtered. The filtate was concentrated and purified by column chromatograph in silica gel, using the eluent of 0-6% ethyl acetate in hexane. The fractions containing product were collected and concentrated to give a suspension. The solid was collected by filtration to afford a pure product (14.45 g, yield 36.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.37-4.42 (q, 2H), 1.38-1.41 (t, 3H).

[00678] **Step 4:** 3,5-dibromo-4-cyanothiophene-2-carboxylic acid

[00679] Ethyl 3,5-dibromo-4-cyanothiophene-2-carboxylate (6.54 g, 0.0193 mol) was dissolved in a mixture of tetrahydrofuran (40.0 mL, 0.493 mol) and methanol (20.0 mL, 0.494 mol), then sodium hydroxide in water (1.0 M, 60.0 mL, 0.0600 mol) was added at 0°C. The resulting solution was warmed to rt and stirred for 20 min. The mixure was neuturalized with hydrochloric acid in water (4.0 M, 20 mL, 0.080 mol) and extracted with 80 mL DCM twice. The combined organic layesr were washed with 30 mL water, evaporated in vacuo to yield a white solid product (5.96 g, yield 99.4%). LCMS: (FA) ES-, 307, 309, 311.

[00680] **Step 5:** 3,5-Dibromo-4-cyanothiophene-2-carboxamide

[00681] 3,5-Dibromo-4-cyanothiophene-2-carboxylic acid (5.90 g, 18.6 mmol) was added to a solution of thionyl chloride (27.1 mL, 371 mmol) in acetonitrile (40.0 mL, 766 mmol). The mixture was refluxed for 30 min then cooled to rt. The solvent was evaporated in vacuo to dryness to yield a lightly yellow solid. Methylene chloride (100 mL, 2000 mmol) was added to dissolve the solid, then the solution was cooled to 0°C. Under a nitrogen atmosphere, a solution of 0.500 M ammonia in 1,4-dioxane(111.5 mL, 55.7 mmol) was slowly added, and the mixture was brought to room temperature for 1 h. The mixture was evaporated in vacuo to give a solid residue. 100 mL of 1N HCl was added and the suspension was stirred for 1 h at room temperature. The solid product was collected by filtration and dried under high vacuum to give product (5.64 g, yield 98%). LCMS: (FA) ES-, 308, 310, 312.

[00682] **Step 6:** 2,4-Dibromo-5-(4H-1,2,4-triazol-3-yl)thiophene-3-carbonitrile

[00683] 3,5-Dibromo-4-cyanothiophene-2-carboxamide (5.90 g, 19.0 mmol) was suspended in dry Toluene (250 mL, 2300 mmol). 1,1-Dimethoxy-N,N-dimethylmethanamine (10.1 mL, 76.1 mmol) was added and the mixture ws heated to 90°C for 1 hour. The mixture was cooled to rt then rotavaped to dryness to give a crude intermediate. The intermediate was suspended in acetic acid (150 mL, 2600 mmol). Hydrazine hydrate (5.78 mL, 76.1 mmol) was added dropwise and the temperature was raised to 55°C. The mixture was stirred at the same temperature for 2 hours. The suspension was then evaporated to remove most of acetic acid. The resulting solid was collected by filtration and dried under vaccumn to

give a product (5.54 g, yield 87.2%). LCMS: (FA) ES-, 331, 333, 335. ^{1}H NMR (300 MHz, *d6*-dmso) δ: 14.2 (s, br, 1H), 8.65 (s, 1H).

[00684] **Step 7:** 2,4-Dibromo-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile

[00685] 2,4-Dibromo-5-(4H-1,2,4-triazol-3-yl)thiophene-3-carbonitrile (0.80 g, 2.4 mmol) was placed in a 500 mL round bottom flask and tetrahydrofuran (50 mL, 600 mmol) was added. To the resulting solution were added dihydropyran (1.31 mL, 14.4 mmol) and p-toluenesulfonic acid monohydrate (0.683 g, 3.59 mmol). The mixture was stirred for 3h at rt. The solution was then poured into 20 mL water and extracted with 40 mL ethyl acetate twice. The combined organic layers were evaporated in vacuo. The residue was purified by column chromtagraphy using 0-35% EtOAc in hexane to afford a solid product (0.842 g, yield 84%). LCMS: (AA) ES+, 417, 419, 421. ^{1}H NMR (300MHz, $CDCl_3$) δ: 8.38 (s, 1H), 5.55-5.60 (m, 1H), 4.06-4.10 (m, 1H), 3.68-3.78 (m, 1H), 2.15-2.28 (m, 1H), 2.01-2.13 (m, 2H), 1.66-1.80 (m, 3H).

[00686] **Step 8:** 4-Bromo-2-pyridazin-4-yl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile

[00687] A mixture of 2,4-dibromo-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile (0.248 g, 0.594 mmol), 4-(tributylstannyl)pyridazine (2.30 mg, 0.624 mmol), copper(I) iodide (34.0 mg, 0.178 mmol), lithium chloride (75.6 mg, 1.78 mmol) and tetrakis(triphenylphosphine)palladium(0) (34.3 mg, 0.0297 mmol) in dry 1,4-dioxane (5.0 mL, 64 mmol) was sonicated under a nitrogen atmosphere for 2 min then heated in a capped vial to 130°C in microwave machine for 20 mins. The suspension was cooled to rt, diluted with 20% MeOH/DCM (~100 mL), treated with 12 g of silica gel then rotavaped and dried under high vacuum. The coated silica gel was chromatographed on a silica column eluting with MeOH/DCM (0/100 to 5/95) to afford a solid product (0.143 g, yield 57.7%). LCMS: (AA) ES+, 417, 419. ^{1}H NMR (300MHz, $CDCl_3$) δ: 9.55 (s, 1H), 9.37-9.39 (m, 1H), 8.40 (s, 1H), 7.69-8.00 (m, 1H), 5.55-5.60 (m, 1H), 4.08-4.13 (m, 1H), 3.73-3.81 (m, 1H), 2.18-2.30 (m, 1H), 2.03-2.16 (m, 2H), 1.68-1.82 (m, 3H).

[00688] **Step 9:** 4-(2-Naphthylmethyl)-2-pyridazin-4-yl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile.

[00689] Bis(tri-t-butylphosphine)palladium(0) (4.92 mg, 0.00963 mmol), 4-bromo-2-pyridazin-4-yl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile (0.0402 g, 0.0963 mmol), 2-naphthylmethylzinc bromide in tetrahydrofuran (0.50M, 0.578 mL, 0.289 mmol) and tetrahydrofuran (4.0 mL, 49 mmol) were added to a microwave tube. The tube was sealed under a nitrogen atmosphere and heated at 70°C for 2 h then cooled to rt. The mixture was concentrated in vacuo and the residue was

purified by chromatography on a silica gel column eluting with 0-100% EtOAc in hexane to afford a solid product (0.0332 g, yield 72 %). LCMS: (AA) ES+, 479. ^{1}H NMR (300MHz, *d4*-methanol) δ: 9.63 (s, 1H), 9.28-9.35 (m, 1H), 8.68 (s, 1H), 8.13-8.15 (m, 1H), 7.69-8.00 (m, 4H), 7.37-7.48 (m, 3H), 5.62-5.66 (m, 1H), 3.94-4.08 (m, 1H), 3.69-3.80 (m, 1H), 3.30 (s, 2H), 2.07-2.22 (m, 1H), 1.95-2.07 (m, 2H), 1.61-1.79 (m, 3H).

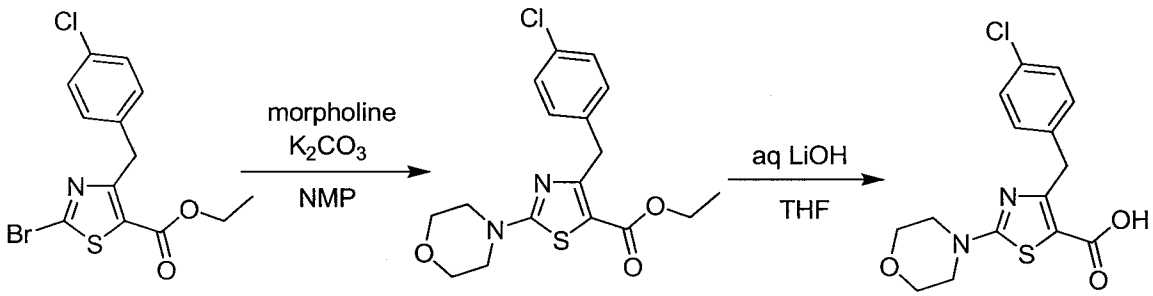
[00690] **Step 10:** 4-(2-naphthylmethyl)-2-pyridazin-4-yl-5-(4H-1,2,4-triazol-3-yl)thiophene-3-carbonitrile (Compound **88**)

[00691] 4-(2-Naphthylmethyl)-2-pyridazin-4-yl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile (0.03178 g, 0.06641 mmol) was dissolved in methanol (3.00 mL, 74.0 mmol). HCl in water (12 M, 3.00mL, 36.0 mmol) was added. The solution was heated at 50°C for 60 min then cooled to rt. The mixture was evaporated in vacuo to remove the most of methanol. To the residue was added 30 mL saturated sodium bicarbonate solution, extracted with 40 mL ethyl acetate twice. The combined EtOAc layers were washed with 20 mL water then concentrated in vacuo. The resulting crystalline solid was collected by filtration to afford a pure product (0.0158 g, yield 60.3%). LCMS: (AA) ES+ 395. ^{1}H NMR (300MHz, *d4*-methanol) δ: 9.60 (s, 1H), 9.27-9.29 (m, 1H), 8.47 (s, 1H), 8.09-8.11 (m, 1H), 7.69-7.77 (m, 4H), 7.37-7.47 (m, 3H), 3.30 (s, 2H).

[00692] The compound in the following table was prepared from the appropriate starting materials in a method analogous to that of Example 27:

89	LCMS: (FA) ES+ 379, 381.

[00693] **Example 28: Synthesis of 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylic acid (Compound 91)**



[00694] **Step 1, Preparation of ethyl 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylate.**

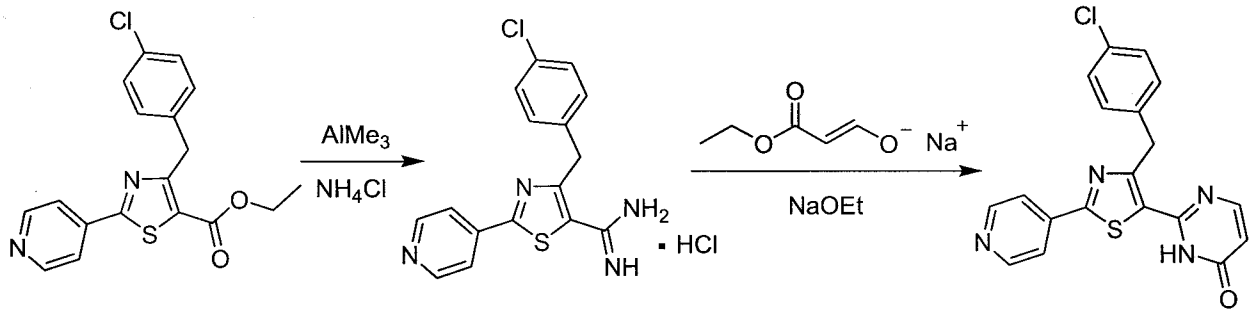
[00695] To a solution of ethyl 2-bromo-4-(4-chlorobenzyl)thiazole-5-carboxylate (4.19 g, 11.6 mmol, prepared as described in Example 10) in N-methylpyrrolidinone (12.2 mL) was added potassium carbonate (3.21 g, 23.2 mmol) and morpholine (1.52 mL, 17.4 mmol) and the resulting mixture was heated to 130 degrees for 90 minutes. The reaction was cooled and the volatiles were removed by

concentration at 65 degrees under oil pump vacuum. The residue was taken up in DCM (100 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with DCM (50 mL). The combined DCM layers were dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was purified by silica gel chromatography (ethyl acetate/hexane = 0/100→35/65) to give 3.44 g of the title compound as a white solid. (80 % yield). LC/MS (FA) ES+ 367. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32-7.27 (m, 2H), 7.24-7.20 (m, 2H), 4.28 (s, 2H), 4.27 (q, 2H, J = 7.2 Hz), 3.80-3.76 (m, 4H), 3.53-3.48 (m, 4H), 1.32 (t, 3H, J = 7.2 Hz).

[00696] Step 2, Preparation of 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylic acid. (Compound 91)

[00697] To a solution of ethyl 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylate (3.44 g, 9.38 mmol) in THF (53 mL) was added water (26 mL) and 1 N LiOH (28.2 mL, 28.2 mmol) and the resulting mixture was heated to 40 degrees overnight. The reaction was cooled, acidified with 1 N HCl, and extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate layers were dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was purified by silica gel chromatography (methanol/DCM = 0/100→20/80). Recrystallization from ethyl acetate/hexanes gave 1.3 g of the title compound as a white solid. (41 % yield). LC/MS (FA) ES+ 339. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.74 (s, 1H), 7.33-7.30 (m, 2H), 7.26-7.23 (m, 2H), 4.21 (s, 2H), 3.67-3.64 (m, 4H), 3.42-3.40 (m, 4H).

[00698] Example 29: Synthesis of 2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)pyrimidin-4(3H)-one (Compound 92)



[00699] Step 1, Preparation of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboximidamide hydrochloride

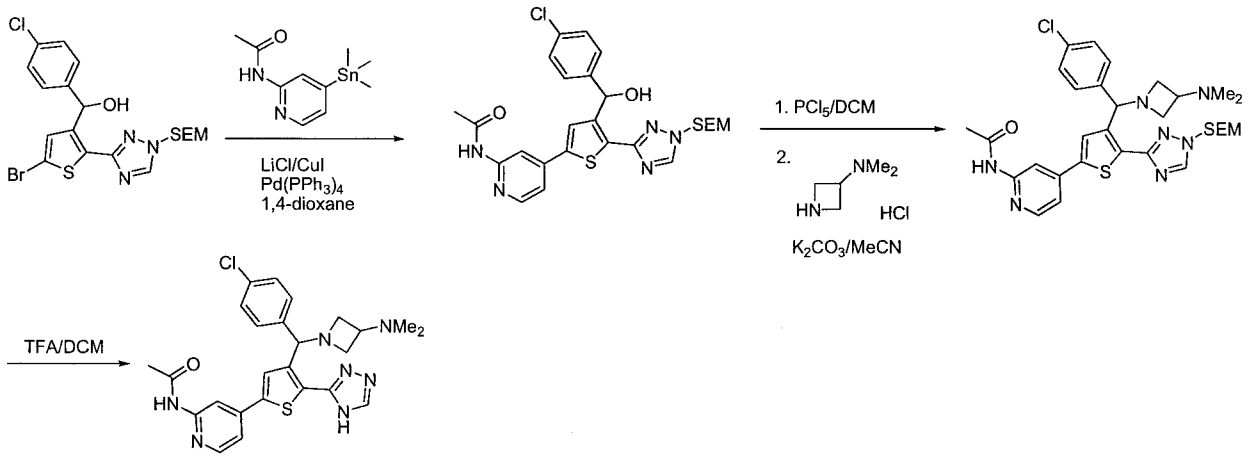
[00700] To a suspension of ammonium chloride (2.25 g, 42.1 mmol) in toluene (21.0 mL) in an ice bath was added 2.0 M trimethylaluminum in toluene (21.1 mL, 42.2 mmol) dropwise (gas evolution). The mixture was then stirred at room temperature for 30 minutes, during which time the solids dissolved. Ethyl 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylate (4.11 g, 11.4 mmol) was added in one portion and the resulting solution was heated slowly to 110 °C over 1 hour, then kept at 110 °C for 2.5 hours. The reaction was allowed to cool to room temperature overnight. The reaction was poured into a

slurry of silica gel (10 grams) in chloroform (100 mL) and stirred 10 minutes. Methanol (20 mL) was added (bubbling occurs), and the mixture was filtered through a short silica gel bed in a sintered glass funnel, eluting with 1:1 methanol/chloroform to remove product. The filtrate was concentrated to give the crude product, which was purified by silica gel chromatography (methanol/chloroform = 50/50) to give 1.9 g of the title compound as a light yellow solid, which is the HCl salt. (45 % yield). (1.6 grams (45%) of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carbonitrile was also recovered) LC/MS (FA) ES+ 329. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.73, (bs, 4H), 8.76-8.74 (m, 2H), 7.90-7.88 (m, 2H), 7.39-7.35 (m, 2H), 7.31-7.27 (m, 2H), 4.30 (s, 2H).

[00701] Step 2, Preparation of 2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)pyrimidin-4(3H)-one (Compound 92)

[00702] To a solution of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboximidamide hydrochloride (188 mg, 0.515 mmol) in ethanol (8.0 mL) was added 21% sodium ethoxide in ethanol (0.192 mL, 0.515 mmol) and sodium 2-ethoxycarbonyl ethenolate (284 mg, 2.06 mmol) (prepared as in J. Med. Chem., (2001), 44(17), 2695-2700), and the reaction was heated to reflux overnight. The reaction was cooled and concentrated. The residue was slurried DCM (15 mL) and water (15 mL) for 20 minutes. The solids were filtered, dried and purified by silica gel chromatography (methanol/DCM = 0/100→15/85) to give the product. HPLC gave 23 mg of the title compound as a yellow solid. (12 % yield). LC/MS (FA) ES+ 381. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.72-8.60 (m, 2H), 8.41 (d, 1 H, J = 5.7 Hz), 7.88-7.85 (m, 2H), 7.40-7.36 (m, 2H), 7.32-7.28 (m, 2H), 6.58 (d, 1H, J = 5.7 Hz), 4.80 (s, 2H).

[00703] Example 30: Synthesis of N-{4-[4-{(4-chlorophenyl)[3-(dimethylamino)azetidin-1-yl]methyl}-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound 181)



[00704] Step 1: Preparation of N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamid

[00705] A mixture of [5-bromo-2-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-3-thienyl](4-chlorophenyl)methanol (3.07 g, 5.52 mmol)) (synthesized in an analogous way as described in Example 2), N-[4-(trimethylstannyl)pyridin-2-yl]acetamide (1.81 g, 6.07 mmol), tetrakis(triphenylphosphine)palladium(0) (319 mg, 0.28 mmol), copper(I) iodide (315 mg, 1.65 mmol) and lithium chloride (702 mg, 16.5 mmol) in 1,4-dioxane (25.0 mL) was stirred at 100 °C for 2 hours under an atmosphere of nitrogen. The reaction was cooled to room temperature and concentrated with Celite. The crude mixture was purified by column chromatography (SiO_2, eluent with methanol in dichloromethane, 0-5% gradient) to afford a yellow solid (2.48 g, 80%). LCMS: (AA) ES+ 556, 558; 1H NMR (400 MHz, $CDCl_3$) δ: 8.48 (br s, 1H), 8.43 (br s, 1H), 8.25 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.33-7.24 (m, 2H), 7.19 (s, 1H), 7.16 (dd, J = 1.2, 5.6 Hz, 1H), 6.22 (s, 1H), 6.05 (br s, 1 H), 5.51 (s, 2H), 3.66 (t, J = 8.4 Hz, 2H), 2.22 (s, 3H), 0.94 (t, J = 8.4 Hz, 2H), -0.01 (s, 9H).

[00706] **Step 2: Preparation of N-{4-[4-{(4-chlorophenyl)[3-(dimethylamino)azetidin-1-yl]methyl}-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide**

[00707] To a solution of N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (100 mg, 0.18 mmol) in dichloromethane (2.00 mL) was added phosphorus pentachloride (112 mg, 0.54 mmol) at room temperature. The mixture was stirred for 15 min and then water (10 mL) was added. The mixture was stirred vigorously for 10 min. The layers were separated and the aqueous layer was extracted with dichloromethane twice. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated in vacuo to give an intermediate as a yellow solid. This intermediate was dissolved in acetonitrile (1.66 mL) and potassium carbonate (124 mg, 0.90 mmol) and 1-azetidin-3-yl-dimethylamine hydrochloride (130 mg, 0.54 mmol) were added. The mixture was stirred at 80 °C for 5 hours. After cooling to room temperature, the mixture was diluted with dichloromethane and filtered through a glass filter. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (SiO_2, elution with methanol in dichloromethane, 0-10% gradient) to afford a solid product (103 mg, 52.3%). LCMS: (AA) ES+ 638, 640; 1H NMR (400 MHz, $CDCl_3$) δ: 8.48 (s, 1H), 8.26 (s, 1H), 8.22 (d, J = 5.2 Hz, 1H), 8.10 (s, 1H), 7.80 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.25-7.21 (m 3H), 5.61 (s, 1H), 5.56 (s, 2H), 3.72 (dd, J = 8.8, 7.6 Hz, 2H), 3.43-3.32 (m, 2H), 2.93-2.80 (m, 3H), 2.24 (s, 3H), 2.06 (s, 6H), 0.99 (dd, J = 8.8, 7.6 Hz, 2H), 0.02 (s, 9H).

[00708] **Step 3: Preparation of N-{4-[4-{(4-chlorophenyl)[3-(dimethylamino)azetidin-1-yl]methyl}-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound 181)**

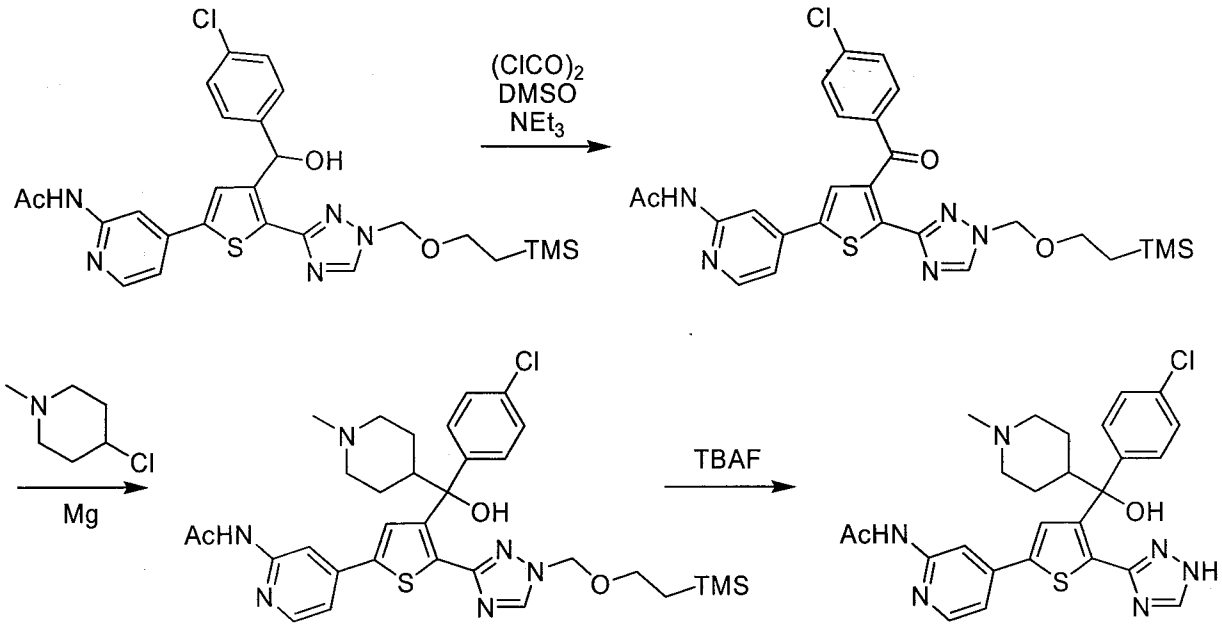
[00709] N-{4-[4-{(4-chlorophenyl)[3-(dimethylamino)azetidin-1-yl]methyl}-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (60 mg, 0.094 mmol) was dissolved in dichloromethane (1.19 mL) and trifluoroacetic acid (0.30 mL, 3.85 mmol) was added. The mixture was stirred at room temperature overnight. The mixture was concentrated in vacuo and distributed between EtOAc and saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, elution with methanol in dichloromethane, 0-20% gradient) to afford the title compound as a white solid (34.2 mg, 71.6%). LCMS: (AA) ES+ 508, 510; 1H NMR (400 MHz, d_4-methanol): 8.51 (s, 1H), 8.39 (s, 1H), 8.24 (br s, 1H), 7.78 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.32 (br s, 1H), 7.26 (d, J = 8.4 Hz, 2H), 5.71 (s, 1H), 3.45-3.36 (m, 2H), 3.00-2.83 (m, 3H), 2.19 (s, 3H), 2.06 (s, 6H).

[00710] The compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 30:

129	LCMS: (AA) ES+ 494, 496.
144	LCMS: (AA) ES+ 508, 510.
157	LCMS: (AA) ES+ 576, 578.
160	LCMS: (AA) ES+ 508, 510.
170	LCMS: (AA) ES+ 494, 496.
172	LCMS: (AA) ES+ 479.
189	LCMS: (AA) ES+ 450, 452.
211	LCMS: (AA) ES+ 451, 453.
218	LCMS: (AA) ES+ 519, 521.
222	LCMS: (AA) ES+ 522, 524.
223	LCMS: (AA) ES+ 509, 511.
226	LCMS: (AA) ES+ 469, 471.
227	LCMS: (AA) ES+ 463, 465.
230	LCMS: (AA) ES+ 479, 481.
244	LCMS: (FA) ES+ 467, 469.

245	LCMS: (AA) ES+ 536, 538.
250	LCMS: (AA) ES+ 408, 410.
269	LCMS: (AA) ES+ 509, 511.
274	LCMS: (AA) ES+ 494, 496.
277	LCMS: (AA) ES+ 494, 496.

[00711] Example 31: Synthesis of N-(4-{4-[(4-chlorophenyl)(hydroxy)(1-methylpiperidin-4-yl)methyl]-5-(4H-1,2,4-triazol-3-yl)-2-thienyl}pyridin-2-yl)acetamide (Compound 237)



[00712] Step1: A solution of oxalyl chloride (63.1 uL, 0.746 mmol) in methylene chloride (1.50 mL, 23.4 mmol) was cooled to -78 °C. To this solution was added dimethyl sulfoxide (65.1 uL, 0.918 mmol) in methylene chloride (1.00 mL) dropwise. The reaction was stirred for 10min under an atmosphere of Nitrogen. To this mixture was added a solution of N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (319 mg, 0.574 mmol) in methylene chloride (1.50 mL) dropwise. In 1 hr, triethylamine (0.400 mL, 2.87 mmol) was added dropwise to the reaction and the resulting mixture was warmed to rt. In 1 hr, the solution was diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2(x2). The combined org layer was washed with $NaHCO_3$(aq) saturated solution, dried, and concentrated to provide N-{4-[4-(4-

chlorobenzoyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1, 2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide as a yellow solid (325 mg, quantative). LCMS: (AA) 554, 556; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.47 (s, 1H), 8.32 – 8.24 (m, 1H), 8.11 – 8.03 (s, 1H), 8.03 – 7.92 (s, 1H), 7.87 – 7.77 (m, 2H), 7.63 – 7.57 (s, 1H), 7.42 – 7.32 (m, 3H), 5.37 – 5.32 (s, 2H), 3.53 – 3.40 (t, J = 8.1 Hz, 2H), 2.27 – 2.19 (s, 3H), 0.94 – 0.80 (t, J = 8.1 Hz, 2H), 0.02 – -0.04 (s, 9H).

[00713] **Step2**: A 25 mL round bottom flask charged with magnesium turnings (23.0 mg, 0.947 mmol) was flame-dried. To the flask was added tetrahydrofuran (1.00 mL) and a drop of 1,2-dibromoethane. The mixture was heated to 45 °C for 10 min and cooled to rt. To the mixture was added 4-chloro-N-methylpiperidine (126 mg, 0.947 mmol). The reaction was stirred at 35 °C under an atmosphere of nitrogen for 12 hrs. The mixture turned cloudy, and magnesium turnings eventually disappeared, as the reaction progressed. To a solution of N-{4-[4-(4-chlorobenzoyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (113 mg, 0.204 mmol) in tetrahydrofuran (1.00 mL) was added the pre-prepared Grignard reagent solution dropwise at 0 °C. In 3 hrs, the reaction was warmed to rt. In another 3 hrs, the reaction was quenched with water and distributed between $NaHCO_3$(aq) saturated solution and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was dried and concentrated. Purification on a silica gel column (gradient elution, 1-20% MeOH) provided N-(4-{4-[(4-chlorophenyl)(hydroxy)(1-methylpiperidin-4-yl)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl}pyridin-2-yl)acetamide as a yellow solid (59.0 mg, 44.3% yield). LCMS: (AA) ES+ 653, 655; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.66 (s, 1H), 8.60 – 8.49 (s, 1H), 8.31 – 8.23 (d, J = 5.3 Hz, 1H), 8.15 – 8.08 (m, 2H), 7.66 – 7.60 (s, 1H), 7.34 – 7.23 (m, 3H), 7.17 – 7.08 (d, J = 8.7 Hz, 2H), 5.45 – 5.38 (s, 2H), 3.63 – 3.51 (m, 2H), 3.49 – 3.44 (s, 3H), 3.02 – 2.90 (d, J = 10.8 Hz, 1H), 2.90 – 2.78 (d, J = 11.2 Hz, 1H), 2.28 – 2.20 (m, 4H), 2.20 – 2.09 (m, 1H), 2.07 – 1.95 (m, 1H), 1.96 – 1.78 (m, 2H), 1.76 – 1.58 (qd, J = 12.7, 3.8 Hz, 1H), 1.16 – 1.07 (d, J = 12.5 Hz, 1H), 0.99 – 0.85 (m, 2H), 0.02 – -0.04 (s, 9H).

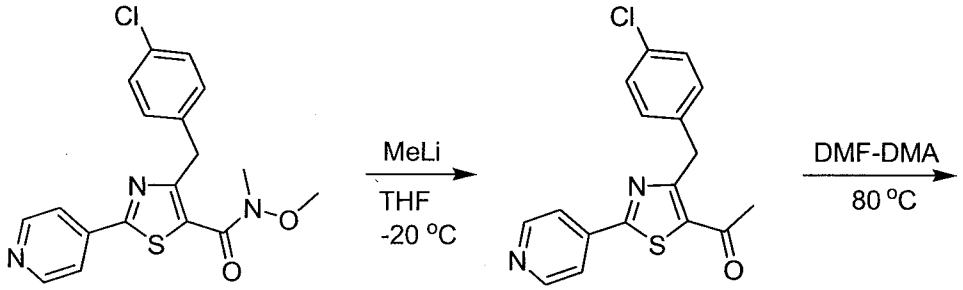
[00714] **Step3**: A 5 mL microwave tube was charged with N-(4-{4-[(4-chlorophenyl)(hydroxy)(1-methylpiperidin-4-yl)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl}pyridin-2-yl)acetamide (10.0 mg, 0.0153 mmol) and tetrahydrofuran (0.500 mL, 6.16 mmol). To the solution was added 1.00

M of tetra-n-butylammonium fluoride in tetrahydrofuran(61.2 uL). The tube was sealed and heated to 80 °C in an oil bath for 4 hrs. The resulting mixture was cooled to rt and distributed between $NaHCO_3$(aq) saturated solution and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined org layer was dried and concentrated. Purification on HPLC (reverse phase, AA) provided N-(4-{4-[(4-chlorophenyl)(hydroxy)(1-methylpiperidin-4-yl)methyl]-5-(4H-1,2,4-triazol-3-yl)-2-thienyl}pyridin-2-yl)acetamide as a white solid. (2.0mg, 25% yield) LCMS (AA) ES+ 523, 525; ^{1}H NMR (400 MHz, MeOD) δ 8.50 – 8.42 (s, 1H), 8.41 – 8.36 (s, 1H), 8.36 – 8.29 (d, J = 5.3 Hz, 1H), 7.92 – 7.83 (s, 1H), 7.50 – 7.43 (m, 1H), 7.43 – 7.34 (d, J = 8.6 Hz, 2H), 7.25 – 7.14 (d, J = 8.6 Hz, 2H), 2.91 – 2.76 (m, 1H), 2.65-2.55 (m, 4H), 2.26 – 2.15 (s, 3H), 2.11 – 2.01 (m, 2H), 1.88 – 1.72 (m, 2H), 1.70 – 1.57 (s, 1H), 1.47 – 1.35 (dd, J = 15.0, 7.4 Hz, 1H), 1.31 – 1.20 (m, 2H).

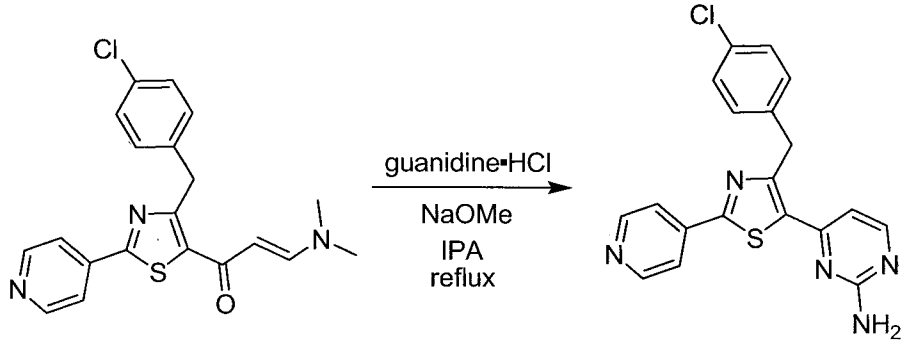
[00715] The compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 31:

145	LCMS: (AA) ES+ 511, 513
225	LCMS: (AA) ES+ 493, 495.
273	LCMS: (AA) ES+ 508, 510.

[00716] Example 32: Synthesis of 4-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)pyrimidin-2-amine (Compound 150)



from example 18



[00717] Step 1, Preparation of 1-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)ethanone

[00718] To a solution of 4-(4-chlorobenzyl)-N-methoxy-N-methyl-2-(pyridin-4-yl)thiazole-5-carboxamide (1.79 g, 4.79 mmol) in THF (97 mL) at -20 °C was added a 1.60 M solution of MeLi in ether (4.19 mL, 6.70 mmol). The reaction was stirred for 30 minutes at -20 °C. An additional portion of a 1.60 M solution of MeLi in ether (0.838 mL, 1.34 mmol) was added and the reaction was stirred for 30 more minutes at -20 °C. The reaction was quenched by adding saturated ammonium chloride (25 mL) followed by water (35 mL). The mixture was extracted with ethyl acetate (2 x 150 mL) and the combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (EA/DCM = 0/100→80/20) to give 1.27 g (81 % yield) of the title compound.as a light yellow solid. LC/MS (FA) ES+ 329, 331. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.75-8.73 (m, 2H), 7.83-7.81 (m, 2H), 7.34-7.31 (m, 2H). 7.26-7.23 (m, 2H), 4.53 (s, 2H), 2.59 (s, 3H).

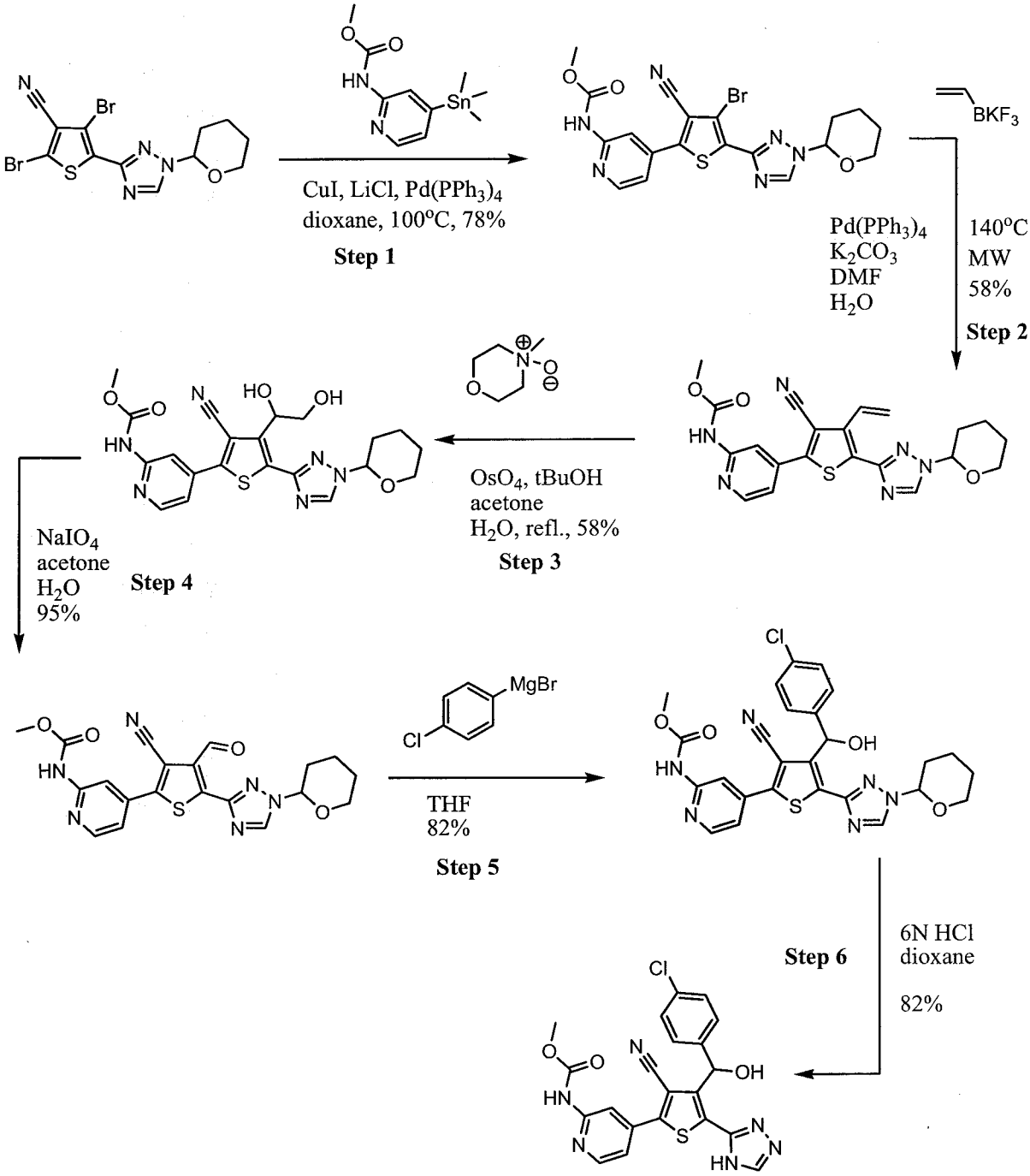
[00719] Step 2, Preparation of (E)-1-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-3-(dimethylamino)prop-2-en-1-one

[00720] A solution of 1-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)ethanone (370 mg, 1.12 mmol) in 1,1-dimethoxy-N,N-dimethylmethanamine (10.0 mL, 75.3 mmol) was heated to 80 degrees for 6 hours. The reaction was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography (EA/DCM = 0/100→100/0) to give 389 mg (90 % yield) of the title compound.as a yellow solid. LC/MS (FA) ES+ 384, 386. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.70-8.68 (m, 2H), 7.81-7.75 (m, 3H), 7.36-7.33 (m, 2H), 7.26-7.24 (m, 2H), 5.41 (d, 1H, J = 12.3 Hz), 4.55 (s, 2H), 3.16 (s, 3H), 2.88 (s, 3H).

[00721] Step 3, Preparation of 4-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)pyrimidin-2-amine

[00722] To a solution of (E)-1-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-3-(dimethylamino)prop-2-en-1-one (93.0 mg, 0.242 mmol) in isopropyl alcohol (1.0 mL) was added guanidine hydrochloride (34.7 mg, 0.363 mmol) and sodium ethoxide (65.4 mg, 1.21 mmol) and the resulting mixture was heated to reflux for 3 days. The reaction was cooled and concentrated in vacuo. The residue was slurried in DCM (10 mL) and water (10 mL). The undissolved solids were filtered. This material was purified by preparative reverse phase chromatography to give 57 mg (62 % yield) of the title compound as a white solid. LC/MS (FA) ES+ 380, 382. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.73-8.71 (m, 2H), 8.31 (d, 1H, J = 5.1 Hz), 7.88-7.86 (m, 2H), 7.36-7.30 (m, 4H), 6.86 (bs, 2H), 6.84 (d, 1H, J = 5.1 Hz), 4.56 (s, 2H).

[00723] Example 33: Synthesis of Methyl {4-[4-[(4-chlorophenyl)(hydroxy)methyl]-3-cyano-5-(4H-1,2,4-triazol- 3-yl)-2-thienyl]pyridin-2-yl}carbamate (Compound 195)



[00724] Step 1: Methyl (4-{4-bromo-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate

[00725] A mixture of 2,4-dibromo-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile (1.27 g, 3.05 mmol), methyl [4-(trimethylstannyl)pyridin-2-yl]carbamate (0.960 g, 3.05 mmol), lithium chloride (0.388 g, 9.14 mmol), copper(I) iodide (0.174 g, 0.914 mmol) and tetrakis(triphenylphosphine)platinum (0) (0.190 g, 0.152 mmol) in anhydrous 1,4-dioxane (45 mL) was

degassed by evacuation in vacuum and backfilling with N_2 4 times, then heated to 100°C under N_2 for 8 hours, then cooled to room temperature. The suspension was filtered and washed with dioxane. The solid was suspensded in 20% MeOH in DCM (300 mL), and washed with water (2X). The organic suspension was concentrated in a rotavapor to give a solid residue. The residue was stirred in DMF/DCM (10 mL / 10 mL) at room temperature for 20 min, filtered and washed with DCM to give a solid product (1.16 g, yield 77.8%). LC/MS: (FA) ES+ 489, 491. ^{1}H NMR (400MHz, d_4-MeOH /*d*-chloroform) δ 8.26-8.35 (m, 3H), 7.34 (m, 1H), 5.48 (m, 1H), 4.00 (m, 1H), 3.73 (s, 3H), 3.64-3.69 (m, 1H), 1.97-2.14 (m, 3H), 1.58-1.68 (m, 3H).

[00726] Step 2: Methyl (4-{3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-4-vinyl-2-thienyl}pyridin-2-yl)carbamate

[00727] A mixture of methyl (4-{4-bromo-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate (1.14 g, 2.33 mmol) , potassium vinyltrifluoroborate (0.624 g, 4.66 mmol), tetrakis(triphenylphosphine)platinum (0) (0.145 g, 0.116 mmol) and potassium carbonate (0.967 g, 7.00 mmol) in N,N-dimethylformamide (14.0 mL) and water (5.0 mL) in a microwave vial was heated under nitrogen atmosphere at 140°C in a microwave for 15 min. The mixture was cooled to room temperature, quenched with water, extracted with DCM, washed with water then brine, dried over Na_2SO_4, filtered and rotavaped to give a crude product. Purification on a silica gel column using MeOH/DCM (0/100 to 5/95) afforded the desired product (1.16 g, with PPh3 and O=PPh3 contaminated) with Rf on TLC (MeOH/DCM 5/95) of 0.4, and de-carbamide product (0.627 g, yield 58%). LC/MS: (FA) ES+ 437. ^{1}H NMR (400MHz, *d*-chloroform) δ 8.52 (s, 1H), 8.45 (s, 1H), 8.41 (m, 1H), 8.33 (s, 1H), 7.51-7.59 (m, 1H), 7.46 – 7.49 (m, 1H), 6.28-6.33 (m, 1H), 5.66-5.69 (m, 1H), 5.51-5.54 (m, 1H), 4.09-4.12 (m, 1H), 3.86 (s, 3H), 3.75-3.78 (m, 1H), 2.00-2.20 (m, 3H), 1.68-1.77 (m, 3H).

[00728] Step 3: Methyl (4-{3-cyano-4-(1,2-dihydroxyethyl)-5-[1-(tetrahydro-2H-pyran-2-yl)- 1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate

[00729] To the suspension of methyl (4-{3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-4-vinyl-2-thienyl}pyridin-2-yl)carbamate (0.625 g, 1.34 mmol) in tert-butyl alcohol (3.0 mL) and acetone (30 mL) was added N-methylmorpholine N-oxide (0.315 g, 2.69 mmol), followed by water (1.0 mL) then 0.157 M of osmium tetraoxide in Water(0.257 mL, 0.0404 mmol). The pale yellow suspension was stirred at room temperature for 17 hours. N-Methylmorpholine N-oxide (0.315 g, 2.69 mmol) was added and the suspension was stirred for 3 more hours, then heated to reflux for 7 hours. The mixture was cooled to room temperature, rotavaped and azeotroped with MeOH to give a solid crude residue. The crude solid was partially dissolved in DCM-MeOH, coated on silica gel, evaporated in rotavapor and chromatographed in a silica gel column using an elution of MeOH/DCM (0/100 to 5/95) to afford a solid product (0.365 g, yield 57.6 %). LC/MS: (FA) ES+ 471; ES- 469, . ^{1}H NMR (400MHz, *d*-

chloroform/*d4*-methanol) δ 8.35 (m, 2H), 8.30 (m, 1H), 7.40 (m, 1H), 5.47-5.49 (m, 1H), 5.31-5.33 (m, 1H), 4.03-4.07 (m, 1H), 3.87 (m, 1H), 3.79 (s, 3H), 3.71-3.81 (m, 2H), 2.13 (m, 1H), 2.00-2.02 (m, 2H), 1.65-1.70 (m, 3H).

[00730] Step 4: Methyl (4-{3-cyano-4-formyl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate

[00731] Methyl (4-{3-cyano-4-(1,2-dihydroxyethyl)-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate (0.362 g, 0.769 mmol) was dissolved in acetone (40 mL) and water (10 mL). Sodium metaperiodate (0.494 g, 2.31 mmol) was added and the mixture was stirred at room temperature for 6 hours. Sodium metaperiodate (0.329 g, 1.54 mmol) was added and the mixture was stirred for 16 more hours. The mixture was concentrated in rotavapor. The residue was triturated with water, filtered and washed throughly with water, then dried in lyophilizer to give a dry solid product (0.320 g, yield 94.8%). LC/MS: (FA) ES+ 439. ^{1}H NMR (400MHz, *d6*-dmso) δ 10.67 (s, 1H), 10.57 (s, 1H), 9.05 (s, 1H), 8.49 (m, 1H), 8.28 (s, 1H), 7.50 (m, 1H), 5.69-5.73 (m, 1H), 3.94-3.98 (m, 1H), 3.73 (s, 3H), 3.66-3.71 (m, 1H), 1.93-2.12 (m, 3H), 1.58-1.71 (m, 3H).

[00732] Step 5: Methyl (4-{4-[(4-chlorophenyl)(hydroxy)methyl]-3-cyano-5-[1-(tetrahydro- 2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate

[00733] To a suspension of methyl (4-{3-cyano-4-formyl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate (0.1077 g, 0.2456 mmol) in anhydrous Tetrahydrofuran (6.0 mL) cooled with ice bath was added slowly 1.0 M of 4-chlorophenylmagnesium bromide in ether(2.50 mL, 2.50 mmol). The resulting clear solution was stirred with cooling for 30 min, then the mixture was quenched with methanol (0.5 mL), then with acetic acid (148 mg, 2.46 mmol) . The mixture was warmed to room temperature, then rotavaped to give crude product, which was chromatograph in a silica gel column using MeOH/DCM (0/100 to 3/97) to afford a solid product (0.116 g, yield 82%). LC/MS: (FA) ES+ 551; ES- 549, . ^{1}H NMR (400MHz, *d*-chloroform/*d4*-methanol) δ 8.36 (s, 1H), 8.29 (m, 2H), 7.43 (m, 1H), 7.34 (m, 2H), 7.19 (m, 2H), 6.37 (s, 1H), 5.41-5.46 (m, 1H), 3.99-4.04 (m, 1H), 3.79 (s, 3H), 3.68-3.72 (m, 1H), 2.13 (m, 1H), 1.97-2.00 (m, 2H), 1.55-1.70 (m, br, 3H).

[00734] Step 6: Methyl {4-[4-[(4-chlorophenyl)(hydroxy)methyl]-3-cyano-5-(4H-1,2,4-triazol- 3-yl)-2-thienyl]pyridin-2-yl}carbamate

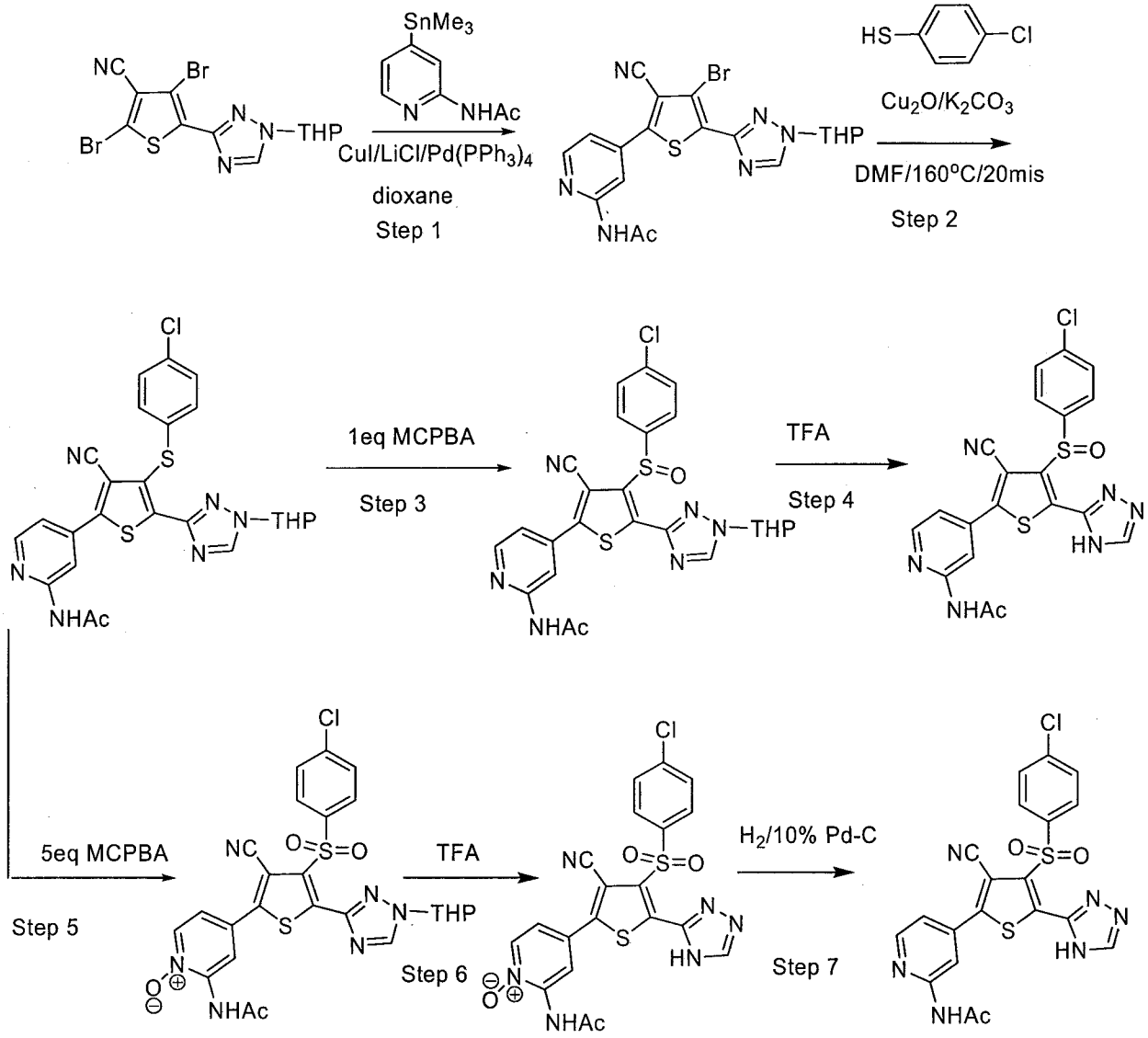
[00735] To a suspension of methyl (4-{4-[(4-chlorophenyl)(hydroxy)methyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate (0.0450 g, 0.0817 mmol) in 1,4-dioxane (4.0 mL, 51 mmol) and cooled in an ice bath was added 6.0 M hydrochloric acid in water (4.0 mL, 24 mmol). The resulting solution was brought to room temperature. Hexane (5.0 mL) was added and the bi layer mixture was stirred for 4 hours. The hexane was separated and the aqueous layer

was washed with hexane twice. The aqueous layer was concentrated on a rotavapor to ~ half volume, diluted with ice and water, basified with saturated aqueous $NaHCO_3$ to pH ~ 7.5, extracted with EtOAc (4 x). The combined EtOAc solutions were washed with brine, dried over Na_2SO_4, filtered, and rotavaped to give a crude solid. The crude solid was chromatographed on a silica gel column using MeOH/DCM (0/100 to 5/95) to afford a solid product (33 mg, yield 82 %). LC/MS: (FA) ES+ 467, 469. ^{1}H NMR (400MHz, *d6*-dmso) δ 10.50 (s, 1H), 8.82 (s, 1H), 8.41 (m, 1H), 8.20 (s, 1H), 7.57 (m, 2H), 7.39 (m, 3H), 7.06 (s, 1H), 6.59 (s, br, 1H), 3.69 (s, 3H).

[00736] The compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 33:

153	LCMS: (AA) ES+ 468.
165	LCMS: (AA) ES+ 451, 453.

[00737] Example 34: Synthesis of N-{4-[4-[(4-chlorophenyl)sulfinyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound 131) and N-{4-[4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound 140)



[00738] Step 1: N-(4-{4-bromo-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)acetamide

[00739] A mixture of 2,4-dibromo-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile (1.3809 g, 3.3027 mmol), [B] N-[4-(trimethylstannyl)-pyridin-2-yl]acetamide (987.38 mg, 3.3028 mmol), copper(I) iodide (188.70 mg, 0.99082 mmol), lithium chloride (420.04 mg, 9.9082 mmol) and tetrakis(triphenylphosphine)-palladium(0) (190.82 mg, 0.16514 mmol) in dry 1,4-Dioxane (20.0 mL) was sonicated under N_2 for 2 min, then heated in a capped vial to 130°C in microwave machine for 20 mins. The suspension was cooled to room temperature, and the resudue was purified using silica gel chromatography. The eluent was 40-100% ethyl acetate in hexane, affording a solid product (0.8802g, yield 56.3%) LCMS: (AA) ES+ 473, 475. 1H NMR (300MHz, CDCl3) δ: 8.61

(s, 1H), 8.41 (d, 1H), 8.39 (s, 1H), 8.10 (s, 1H), 7.53 (d, 1H), 5.55-5.60 (dd, 1H), 4.06-4.10 (m, 1H), 3.68-3.78 (m, 1H), 2.35 (s, 3H), 2.15-2.28 (m, 1H), 2.01-2.13 (m, 2H), 1.66-1.80 (m, 3H).

[00740] **Step 2**: N-(4-{4-[(4-chlorophenyl)sulfanyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)acetamide

[00741] N-(4-{4-bromo-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)acetamide (0.2601 g, 0.5495 mmol), copper(I) oxide (0.1572 g, 1.099 mmol), 4-chlorobenzenethiol (0.3179 g, 2.198 mmol) and potassium carbonate (0.2278 g, 1.648 mmol) were added to a microwave vial followed by DMF (15.00 mL). The reaction was irradiated at 150 °C for 15 mins. The solid was filtered and washed with DCM. The solution was diluted with 80 ml water, and extracted with 100 ml DCM for two times. The organic layer was concentrated, and purified by column. The eluent was 50-100% ethyl acetate in hexane to yield a solid product (0.224g, yield 76.0%) LCMS: (AA) ES+ 537, 539. 1H NMR (300MHz, CDCl3) δ: 8.59 (s, 1H), 8.37 (d, 1H), 8.36 (s, 1H), 8.03 (s, 1H), 7.53 (d, 1H), 7.32 (d, 2H), 7.22 (d, 2H), 5.50-5.55 (dd, 1H), 4.02-4.08 (m, 1H), 3.68-3.78 (m, 1H), 2.25 (s, 3H), 2.10-2.18 (m, 1H), 2.00-2.07 (m, 2H), 1.66-1.80 (m, 3H).

[00742] **Step 3**: N-(4-(4-(4-chlorophenylsulfinyl)-3-cyano-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-2-yl)pyridin-2-yl)acetamide

[00743] N-(4-{4-[(4-chlorophenyl)sulfanyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)acetamide (0.0575 g, 0.107 mmol) was dissolved in methylene chloride (5.00 mL), followed by addition of m-chloroperbenzoic acid (0.0194 g, 0.112 mmol). The reaction mixture was stirred at room temperature for 1 hr. The solution was concentrated, and purified by column chromatography. The eluent was 50-100% ethyl acetate in hexane to yield a solid product (0.0324g, 54.7%) LCMS: (AA) ES+ 553, 555. 1H NMR (300MHz, CDCl3) δ: 8.47 (m, 2H), 8.41 (s, 1H), 8.36 (d, 1H), 8.06 (dd, 2H), 7.46 (dd, 2H), 7.45 (d, 1H), 5.53-5.59 (dd, 1H), 4.08-4.16 (m, 1H), 3.73-3.81 (m, 1H), 2.25 (s, 3H), 2.10-2.18 (m, 1H), 2.00-2.07 (m, 2H), 1.69-1.80 (m, 3H).

[00744] **Step 4**: N-{4-[4-[(4-chlorophenyl)sulfinyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound **131**)

[00745] N-(4-(4-(4-chlorophenylsulfinyl)-3-cyano-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-2-yl)pyridin-2-yl)acetamide (0.0315 g, 0.0570 mmol) was dissolved in TFA (5.00 mL, 64.9 mmol). The mixture was stirred at room temperature for 1 hr, and the solvent was evaporated. 10 ml DCM was added to redissolve the material followed by the addition of triethylamine (1 mL). The solvent was evaporated off, and the mixture was purified by silica gel column. The eleuent was 0-6% methanol in hexane to yield a solid product (0.0112g, yield 41.9%) LCMS: (AA) ES+ 469, 471.

1H NMR (300MHz, MeOD) δ: 8.65 (s, 1H), 8.51 (s, 1H), 8.42 (d, 1H), 8.06 (d, 2H), 7.58 (d, 2H), 7.44 (dd, 1H), 2.25 (s, 3H).

[00746] **Step 5:** N-(4-{4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}-1-oxidopyridin-2-yl)acetamide

[00747] N-(4-{4-[(4-chlorophenyl)sulfanyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)acetamide (0.0698 g, 0.130 mmol) was dissolved in methylene chloride (6.00 mL) followed by addition of m-Chloroperbenzoic acid (0.08971 g, 0.5199 mmol). The mixture was stirred for 30 mins at room temperature. The solvent was evaporated, and the residue was purified by column chromatography. The eluent was 0-7% methanol in ethyl acetate to yield a solid product (0.0654g, yield 86.0%) LCMS: (AA) ES+ 585, 587. 1H NMR (300MHz, CDCl3) δ: 8.76 (s, 1H), 8.41 (s, 1H), 8.37 (d, 2H), 8.26 (d, 1H), 7.50 (d, 2H), 7.43 (d, 1H), 5.50-5.57 (dd, 1H), 4.03-4.10 (m, 1H), 3.70-3.78 (m, 1H), 2.25 (s, 3H), 2.10-2.18 (m, 1H), 2.00-2.07 (m, 2H), 1.69-1.80 (m, 3H).

[00748] **Step 6:** N-{4-[4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]-1-oxidopyridin-2-yl}acetamide

[00749] N-(4-{4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}-1-oxidopyridin-2-yl)acetamide (0.0742 g, 0.127 mmol) was dissolved in trifluoroacetic acid (4.00 mL, 51.9 mmol). The mixture was stirred at room temperature for 4 hrs, solvent was evaporated and the residue was purified by HPLC to yield a solid product (0.0421g, yield 66.3%) LCMS: (AA) ES+ 501, 503. 1H NMR (300MHz, MeOD) δ: 8.90 (s, 1H), 8.60 (s, 1H), 8.43 (d, 1H), 8.35 (d, 2H), 7.67 (d, 2H), 7.59 (d, 1H), 2.28 (s, 3H).

[00750] **Step 7:** N-{4-[4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound **140**)

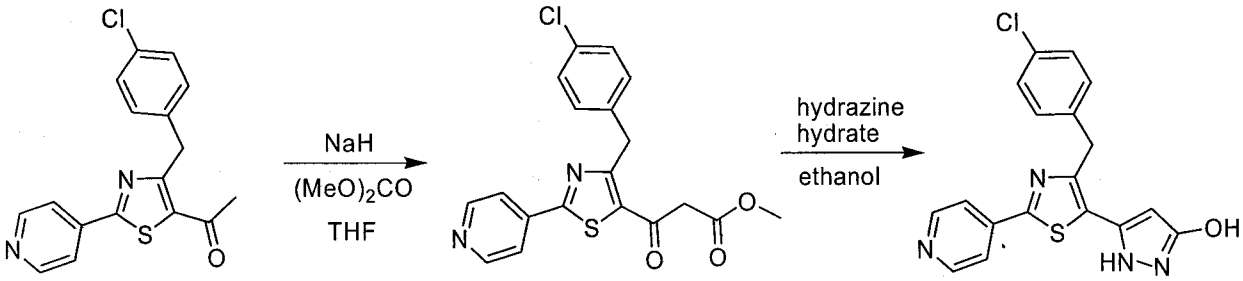
[00751] N-{4-[4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]-1-oxidopyridin-2-yl}acetamide (0.0229 g, 0.0457 mmol) was dissolved in methanol (3.00 mL), followed by the addition of 10% Pd-C (5 mg). The flask was filled with hydrogen at 40 psi, and the suspension was stirred at room temperature for overnight. The solid was filtered off, and the residue was concentrated followed by purification by column chromatography. The eluent was 0-8% methanol in ethyl acetate to yield a solid product (0.0142g, yield 64.0%). LCMS: (AA) ES+ 485, 487. 1H NMR (300MHz, MeOD) δ: 8.60 (s, 1H), 8.53 (s, 1H), 8.45 (d, 1H), 8.35 (d, 2H), 7.66 (d, 2H), 7.48 (d, 1H), 2.20 (s, 3H).

[00752] The compound in the following table was prepared from the appropriate starting materials in a method analogous to that of Example 34:

166	LCMS: (AA) ES+ 454

[00753]

[00754] Example 35: Synthesis of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazol-3-ol (Compound 178)



from example 32

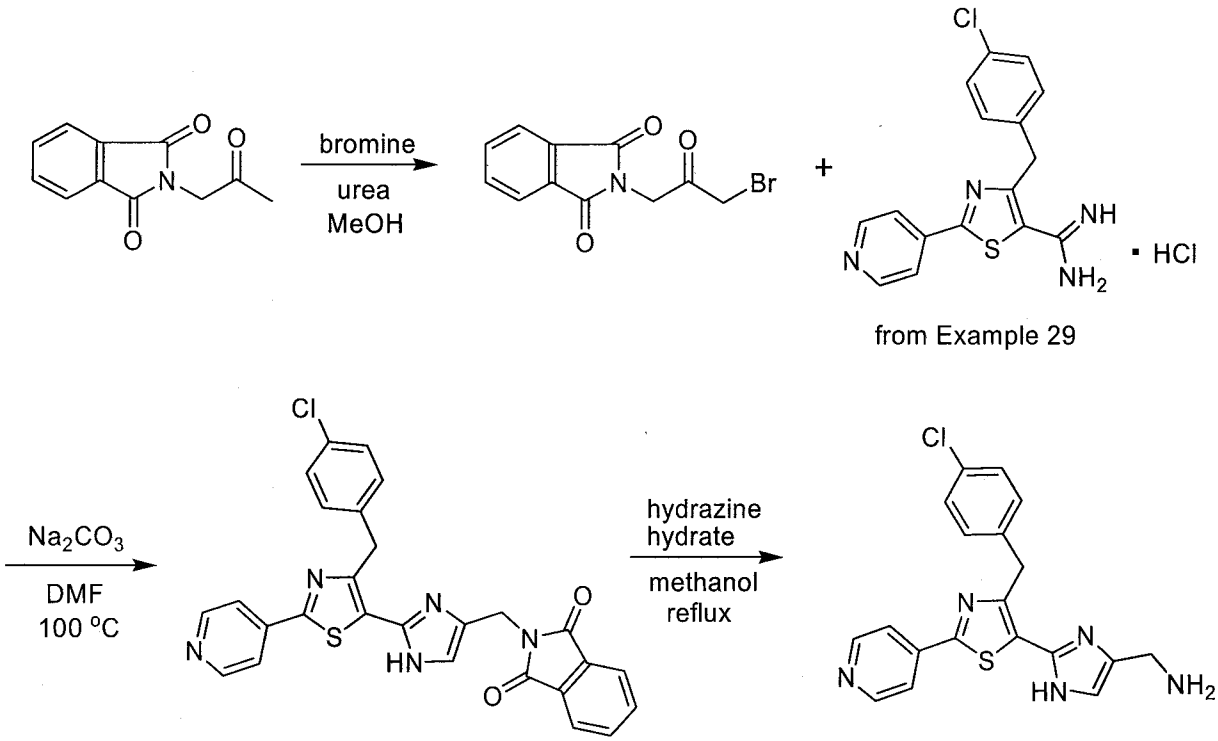
[00755] Step 1, Preparation of ethyl 3-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-3-oxopropanoate

[00756] To a flask containing 60% NaH in mineral oil (213 mg, 5.32 mmol) under nitrogen was added THF (31.7 mL) and carbonic acid, dimethyl ester (0.448 mL, 5.32 mmol). The mixture was heated to 60 degrees and a solution of 1-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)ethanone (875 mg, 2.66 mmol) in THF (12.7 mL) was then added. The mixture was heated at 60 degrees for 1 hour. The reaction was cooled and quenched with methanol (5 mL), then saturated NH_4Cl (10 mL). The organic solvents were concentrated in vacuo, and the aqueous residue was diluted with water (10 mL) and exctracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (EA/DCM = 0/100→40/60) to give 253 mg (25 % yield) of the title compound.as an oil. LC/MS (FA) ES+ 387, 389. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.76-8.74 (m, 2H), 7.83-7.81 (m, 2H), 7.35-7.32 (m, 2H), 7.26-7.23 (m, 2H), 4.53 (s, 2H), 3.89 (s, 2H), 3.77 (s, 3H).

[00757] Step 2, Preparation of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazol-3-ol

[00758] To a solution of ethyl 3-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-3-oxopropanoate (253 mg, 0.631 mmol) in ethanol (16 mL) was added hydrazine hydrate (0.123 mL, 2.52 mmol) and the resulting solution was heated to 80 degrees for 3 hours. The reaction was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→10/90) to give 118 mg of the product. This material was purified by preparative reverse phase chromatography to give 63 mg (27 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 369, 371. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.44 (bs, 1H), 8.68 (bs, 2H), 7.83-7.81 (m, 2H), 7.35-7.32 (m, 2H), 7.27-7.24 (m, 2H), 5.60 (s, 1H), 4.34 (s, 2H).

[00759] Example 36: Synthesis of (2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-imidazol-4-yl)methanamine (Compound 255)



[00760] Step 1, Preparation of 2-(3-bromo-2-oxopropyl)isoindoline-1,3-dione

[00761] To a solution of phthalimidoacetone (4.04 g, 19.9 mmol) in methanol (100 mL) was added urea (1.19 g, 19.9 mmol) and bromine (3.18 g, 19.9 mmol) and the resulting solution was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue taken up in DCM (150 mL) and water (50 mL). The layers were separated and the organic layer was dried, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (EA/hexanes = 0/100→50/50) to give 159 mg (3% yield) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90-7.86 (m, 2H), 7.79-7.73 (m, 2H), 4.78 (s, 2H), 4.01 (s, 2H).

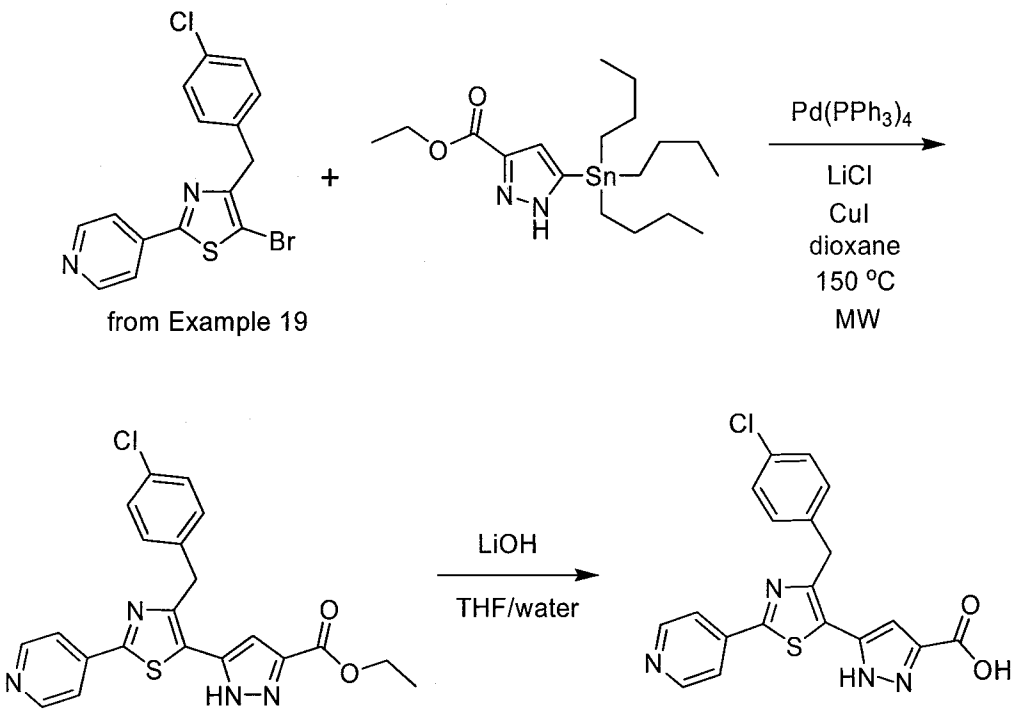
[00762] Step 2, Preparation of 2-((2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-imidazol-4-yl)methyl)isoindoline-1,3-dione

[00763] To a mixture of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboximidamide hydrochloride (112 mg, 0.306 mmol) in DMF (2.96 mL) was added sodium carbonate (162 mg, 1.53 mmol) and 2-(3-bromo-2-oxopropyl)isoindoline-1,3-dione (95.0 mg, 0.337 mmol) and the resulting mixture was heated at 100 degrees for 4 hours. The reaction was cooled and taken up in ethyl acetate (30 mL) and water (5 mL). The layers were separated and the organic layer was washed with water (3 x 5 mL). The organic layer was dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→10/90) to give 47 mg (30% yield) of the title compound. LC/MS (FA) ES+ 512. 514. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.67 (bs, 1H), 8.69-8.67 (m, 2H), 7.91-7.79 (m, 6H), 7.27-7.24 (m, 3H), 7.11-7.08 (m, 2H), 4.77 (s, 2H), 4.45 (s, 2H).

[00764] Step 3, Preparation of (2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-imidazol-4-yl)methanamine

[00765] To a solution of 2-((2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-imidazol-4-yl)methyl)isoindoline-1,3-dione (45 mg, 0.0879 mmol) in methanol (2.0 mL) was added hydrazine hydrate (.0086 mL, 0.176 mmol) and the resulting solution was heated to reflux for 1 hour. The reaction was cooled and concentrated in vacuo. The residue wsa taken up in ethyl acetate and water. The layers were separated and the organic layer was dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→40/60) to give 13 mg (39% yield) of the title compound. LC/MS (FA) ES+ 382, 384. ^{1}H NMR (300 MHz, MeOH-d_4) δ: 8.71-8.68 (m, 2H), 7.82-7.80 (m, 2H), 7.35 -7.29 (m, 4H), 7.22 (s, 1H), 4.53 (s, 2H), 3.86 (s, 2H).

[00766] Example 37: Synthesis of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazole-3-carboxylic acid (Compound 262)



[00767] Step 1, Preparation of ethyl 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazole-3-carboxylate

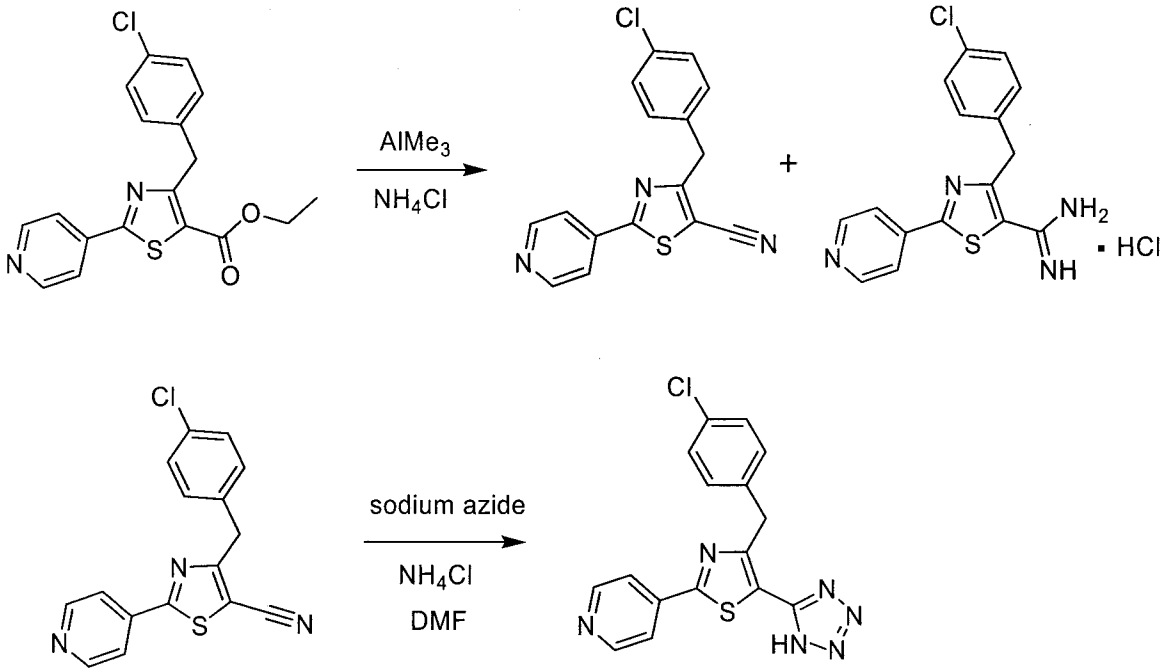
[00768] An argon degassed mixture of 5-bromo-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole (583 mg, 1.59 mmol), ethyl 5-(tributylstannyl)-1H-pyrazole-3-carboxylate (456 mg, 1.06 mmol), tetrakis(triphenylphosphine)palladium(0) (61.4 mg, 0.0531 mmol), copper(I) iodide (60.7 mg, 0.319 mmol), and lithium chloride (135 mg, 3.19 mmol) in dioxane (7.46 mL) was heated in a microwave at 150 degrees for 30 minutes. The reaction mixture was slurried in ethyl acetate (100 mL) and water (2 mL)

and the mixture was filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (EA/DCM = 0/100→100/0) to give the crude product. This material was purified by preparative reverse phase chromatography to give 55 mg (12 % yield) of the title compound as a white solid.LC/MS (FA) ES+ 425, 427. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.71-8.69 (m, 2H), 7.85-7.83 (m, 2H), 7.36-7.33 (m, 2H), 7.28-7.25 (m, 2H), 7.09 (s, 1H), 4.41 (s, 2H), 4.34 (q, 1H, J = 7.2 Hz), 1.31 (t, 1H, J = 7.2 Hz).

[00769] Step 2, Preparation of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazole-3-carboxylic acid

[00770] A solution of ethyl 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazole-3-carboxylate (16.1 mg, 0.0379 mmol) in THF (0.50 mL) was treated with 1.0 M aqueous LiOH (0.0568 mL, 0568 mmol) and the solution was stirred at 40 degrees for 3 days. The reaction was then heated at 65 degrees for 6 hours. The reaction mixture was cooled and acidified with 1N HCl. The solution was extracted with EA (3 x 25 mL) and the combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by preparative reverse phase chromatography to give 1 mg (7 % yield) of the title compound as a white solid. LC/MS (FA) ES+ 397, 399.

[00771] Example 38: Synthesis of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)-5-(1H-tetrazol-5-yl)thiazole (Compound 190)



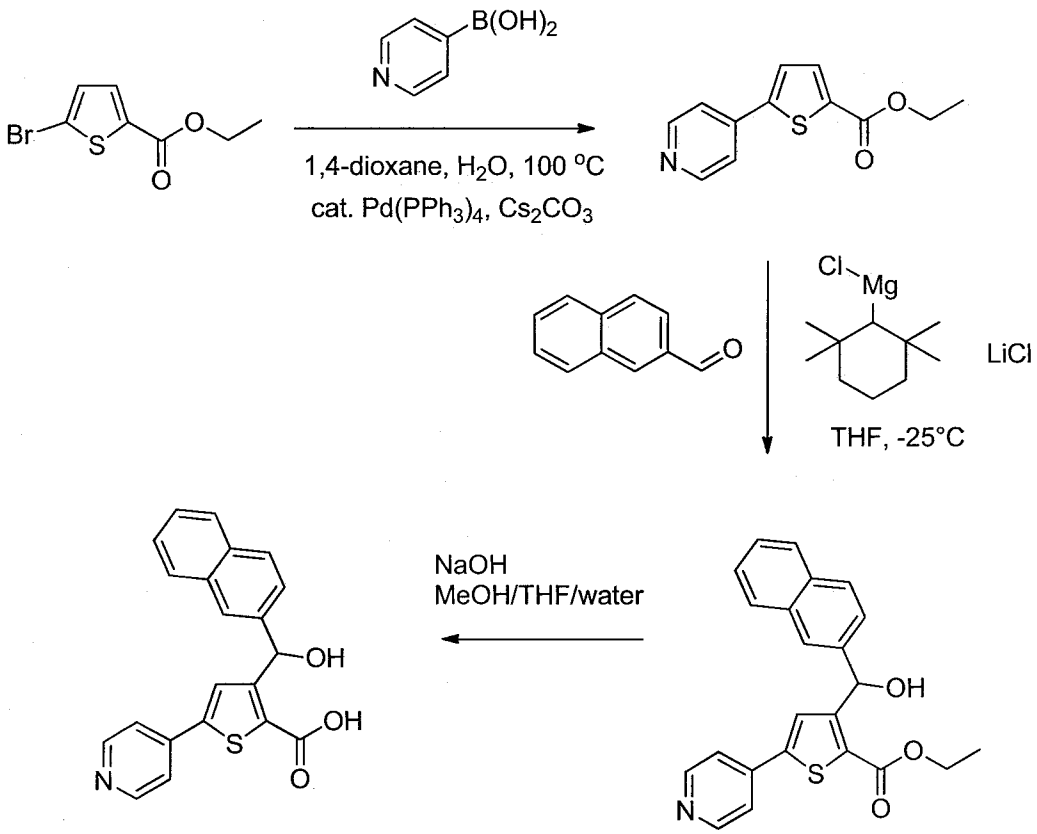
[00772] Step 1, Preparation of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboximidamide hydrochloride and 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carbonitrile

[00773] To a suspension of ammonium chloride (2.25 g, 42.1 mmol) in toluene (21.0 mL) in an ice bath was added 2.0 M trimethylaluminum in toluene (21.1 mL, 42.2 mmol) dropwise (gas evolution was observed). The mixture was then stirred at room temperature for 30 minutes, during which time the solids dissolved. Ethyl 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylate (4.11 g, 11.4 mmol) was added in one portion and the resulting solution was heated slowly to 110 °C over 1 hour, then kept at 110 °C for 2.5 hours. The reaction was allowed to cool to room temperature overnight. The reaction was poured into a slurry of silica gel (10 grams) in chloroform (100 mL) and stirred 10 minutes. Methanol (20 mL) was added (bubbling occured), and the mixture was filtered through a short silica gel bed in a sintered glass funnel, eluting with 1:1 methanol/chloroform to remove product. The filtrate was concentrated to give the crude product, which was purified by silica gel chromatography (MeOH/DCM = 0/100→50/0) to give 1.6 grams (45% yield) of the nitrile, which eluted first, and 1.9 g (45% yield) of the guanidine, which is the HCl salt. Guanidine: LC/MS (FA) ES+ 329. 331. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.73, (bs, 4H), 8.76-8.74 (m, 2H), 7.90-7.88 (m, 2H), 7.39-7.35 (m, 2H), 7.31-7.27 (m, 2H), 4.30 (s, 2H). Nitrile: LC/MS (FA) ES+ 312, 314. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.77-8.75 (m, 2H), 7.78-7.76 (m, 2H), 7.34-7.29 (m, 4H), 4.29 (s, 2H).

[00774] **Step 2, Preparation of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)-5-(1H-tetrazol-5-yl)thiazole**

[00775] To a solution 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carbonitrile (167 mg, 0.536 mmol) in DMF (3.5 mL) was added sodium azide (104 mg, 1.61 mmol) and ammonium chloride (86 mg, 1.61 mmol) and the resulting mixture was heated at 100 degrees overnight. The reaction was cooled and taken up in ethyl acetate and water. The aqueous layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (MeOH/DCM = 0/100→10/90) to give 9 mg (5% yield) of the title compound. LC/MS (FA) ES+ 355, 357. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.74-8.73 (m, 2H), 7.93-7.92 (m, 2H), 7.38-7.32 (m, 4H), 4.62 (s, 2H).

[00776] **Example 39: Preparation of 3-[hydroxy(2-naphthyl)methyl]-5-pyridin-4-ylthiophene-2-carboxylic acid (Compound 205)**



[00777] **Step 1:** Ethyl 5-pyridin-4-ylthiophene-2-carboxylate

[00778] A mixture of ethyl 5-bromothiophene-2-carboxylate (1.560 g, 6.65 mmol), pyridine-4-boronic acid (0.98 g, 7.98 mmol), tetrakis(triphenylphosphine)palladium(0) (768 mg, 0.665 mmol) and cesium carbonate (6.50 g, 19.9 mmol) in 1,4-dioxane (20 mL) and water (3.35 mL) was stirred and heated at 100° C under an atmosphere of nitrogen overnight.The reaction was a clear light orange with a small amount of a second liquid phase on the bottom of the flask. An aliquot was taken, quenched into water, and extracted with ethyl acetate. A TLC on silica gel (1:1 DCM:hexane) indicated that all of the starting material had been consumed. A major new product with Rf ~0.4 was seen. The reaction was cooled to room temperature then was quenched into stirring water and extracted with ethyl acetate. The ethyl acetate extracts were washed with saline, dried over sodium sulfate, filtered, and evaporated to leave crude product as an off-white solid. The crude product was dissolved in minimal DCM then was purified by column chromatography on silica gel (gradient 100% DCM to 50% ethyl acetate) to afford product 1.02g (66% yield) as white solid. LC/MS (FA) ES+ 234. ^{1}H NMR (400 MHz, DMSO) δ 8.68 – 8.60 (m, 2H), 7.91 – 7.83 (m, 2H), 7.78 – 7.71 (m, 2H), 4.37 – 4.27 (d, J = 7.1 Hz, 2H), 1.35 – 1.27 (t, J = 7.1 Hz, 3H).

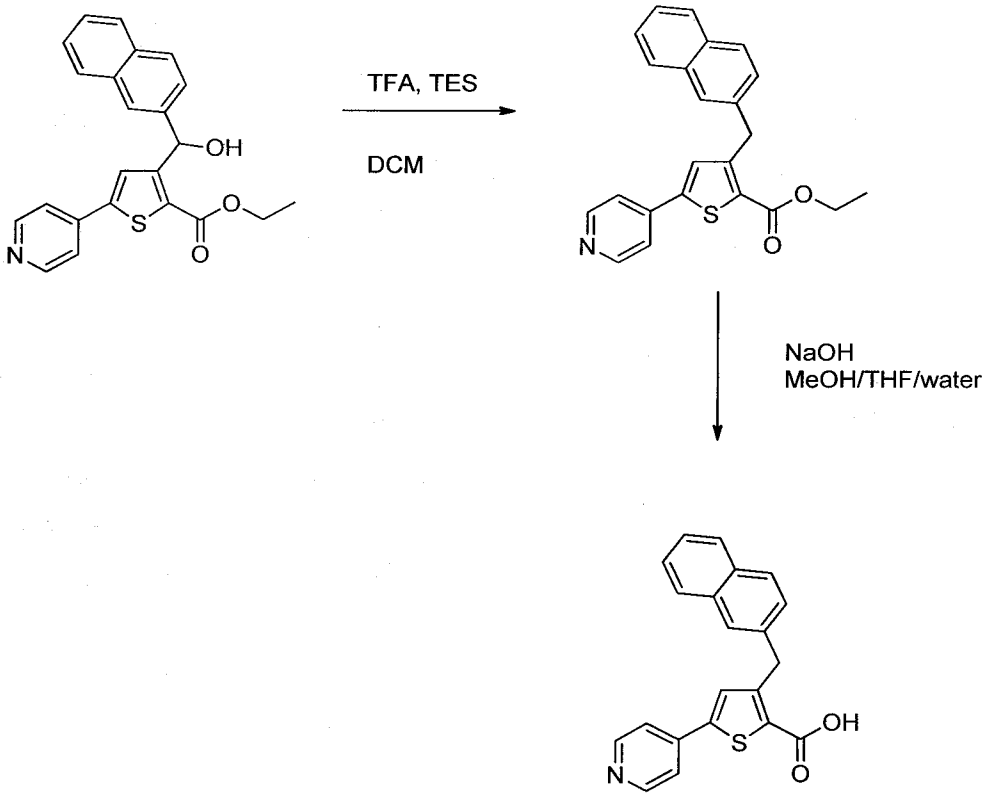
[00779] **Step 2:** Ethyl 3-[hydroxy(2-naphthyl)methyl]-5-pyridin-4-ylthiophene-2-carboxylate

[00780] A dry, nitrogen flushed flask, equipped with a stirbar and septum, was charged with 2,2,6,6-tetramethylpiperidinylmagnesium chloride•lithium chloride in tetrahydrofuran (1.0M, 1.21 mL, 1.21 mmol). The flask was cooled to -25° C and a solution of ethyl 5-pyridin-4-ylthiophene-2-carboxylate (0.257 g, 1.10 mmol) in tetrahydrofuran (1.0 mL, 12 mmol) was added dropwise with stirring. The resulting dark reddish orange solution was stirred at -25° C for 30 minutes. 2-Naphthalenecarboxaldehyde (0.172 g, 1.10 mmol) was then added dropwise (as a solution in 1.5 ml THF) - the reaction mixture became purple. The reaction was stirred at -25° for 5 minutes, then the cooling bath was removed and the reaction was allowed to warm to room temperature with stirring. An aliquot was removed from the reaction and quenched into sat. NH4Cl solution, then extracted with ethyl acetate. A LCMS of this extract indicated that all starting material had been consumed and that the major peak had correct mass for the desired product. The reaction was quenched by the slow dropwise addition of a saturated ammonium chloride solution (5 ml). The resulting yellow-orange mixture was transferred to a separatory funnel and diluted further with water and ethyl acetate. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate. The extracts were combined, washed with saline, dried, and evaporated to leave crude product as an orange oil which was dissolved in minimal dichloromethane then was purified by column chromatography on silica gel (gradient 100% DCM to 5% MeOH in ethyl acetate) to afford product 210 mg (49% yield) as a white foam. LC/MS (FA) ES+ 390. ^{1}H NMR (400 MHz, DMSO) δ 8.63 – 8.58 (dd, J = 4.6, 1.6 Hz, 2H), 8.04 – 8.00 (s, 1H), 8.00 – 7.96 (s, 1H), 7.87 – 7.81 (d, J = 8.7 Hz, 3H), 7.76 – 7.71 (dd, J = 4.6, 1.7 Hz, 2H), 7.62 – 7.58 (d, J = 1.6 Hz, 1H), 7.50 – 7.45 (t, J = 3.0 Hz, 2H), 6.74 – 6.69 (d, J = 4.2 Hz, 1H), 6.33 – 6.28 (d, J = 4.2 Hz, 1H), 4.37 – 4.31 (dd, J = 7.1, 4.3 Hz, 2H), 1.35 – 1.27 (t, J = 7.1 Hz, 3H).

[00781] **Step 3:** 3-[Hydroxy(2-naphthyl)methyl]-5-pyridin-4-ylthiophene-2-carboxylic acid (Compound 205)

[00782] Ethyl 3-[hydroxy(2-naphthyl)methyl]-5-pyridin-4-ylthiophene-2-carboxylate (70.0 mg, 0.180 mmol) was placed in a round bottomed flask equipped with a stirbar. Tetrahydrofuran (2.00 mL), methanol (1.00 mL), and water (1.50 mL) were added with stirring - all solids dissolved. Sodium hydroxide (1.0 M, 1.50 mL, 1.50 mmol) was added in a single portion and the resulting solution was stirred under an atmosphere of nitrogen overnight, resulting in a clear light yellow solution. The reaction was quenched into water and the pH of the mixture was adjusted the pH to ~6-6.5 with sodium bicarbonate solution. The mixture was extracted with ethyl acetate, the extracts were combined and then rotovapped to leave crude product as a light yellow solid. The crude product was purified by HPLC to yield 9 mg (14% yield) product as a pale yellow powder. LC/MS (FA) ES+ 362. ^{1}H NMR (400 MHz, DMSO) δ 8.60 – 8.51 (d, J = 6.1 Hz, 2H), 7.98 – 7.94 (s, 2H), 7.91 – 7.75 (m, 4H), 7.68 – 7.58 (m, 3H), 7.53 – 7.37 (m, 2H), 6.64 – 6.36 (s, 1H).

[00783] Example 40: Preparation of 3-(2-naphthylmethyl)-5-pyridin-4-ylthiophene-2-carboxylic acid (Compound 210)



[00784] **Step 1:** Ethyl 5-pyridin-4-ylthiophene-2-carboxylate

[00785] Ethyl 3-[hydroxy(2-naphthyl)methyl]-5-pyridin-4-ylthiophene-2-carboxylate (118.0 mg, 0.3030 mmol), methylene chloride (2.4 mL), trifluoroacetic acid (140.0 uL, 1.818 mmol), and triethylsilane (84.7 uL, 0.530 mmol) were combined in a round bottomed flask equipped with a stirbar. The reaction was stirred overnight at room temperature under an atmosphere of nitrogen. An aliquot was taken from the reaction, quenched into water, basified with sodium carbonate, and extracted with ethyl acetate. TLC analysis (2:1 ethyl acetate:DCM) indicated that the starting ester was ~50% converted to a slightly higher Rf product. Additional trifluoroacetic acid (300 uL, 4 mmol) and triethylsilane (200 uL, 1 mmol) were added and the reaction was stirred at room temperature under an atmosphere of nitrogen for another 4 hours. LCMS analysis showed one major peak with correct ES+ for product with a small amount of SM remaining. The reaction was quenched into water, basified, and extracted into ethyl acetate. The extract was washed with saline, dried over sodium sulfate, filtered, and evaporated to leave crude product as an oil. The crude product was dissolved in minimal DCM then was purified by column chromatography on silica gel (gradient 100% DCM to 50% ethyl acetate) to afford product 86 mg (76% yield) as a white solid. LC/MS (FA) ES+ 374. ^{1}H NMR (400 MHz, DMSO) δ 8.64 – 8.55 (m, 2H), 7.90

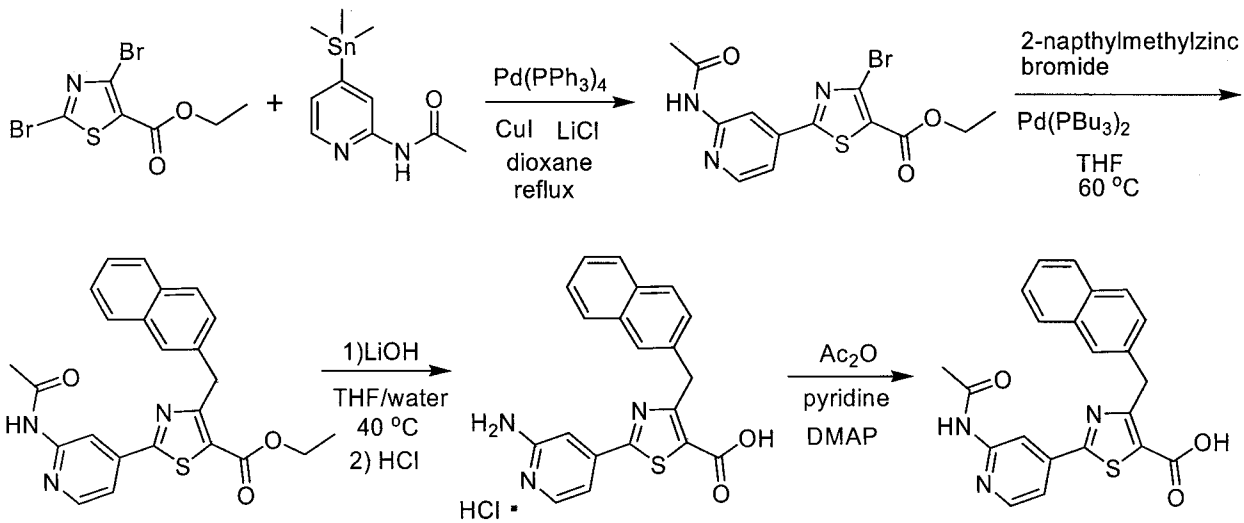
– 7.80 (m, 4H), 7.80 – 7.75 (s, 1H), 7.73 – 7.66 (m, 2H), 7.52 – 7.40 (m, 3H), 4.57 – 4.49 (s, 2H), 4.39 – 4.27 (q, J = 7.1 Hz, 2H), 1.35 – 1.25 (t, J = 7.1 Hz, 3H).

[00786] Step 2: 3-(2-naphthylmethyl)-5-pyridin-4-ylthiophene-2-carboxylic acid (Compound 210)

[00787] Ethyl 3-(2-naphthylmethyl)-5-pyridin-4-ylthiophene-2-carboxylate (80.0 mg, 0.214 mmol) was placed in a round bottomed flask equipped with a stirbar. Methanol (3 mL, 70 mmol) and tetrahydrofuran (3 mL, 40 mmol) were added followed by water (2 mL, 100 mmol). The resulting solution was stirred and lithium hydroxide in water (1.0 M, 0.643 mL, 0.643 mmol) was added. The flask was sealed and stirred overnight at RT. LCMS of an aliquot indicated that all starting material had been consumed to give a single product with the correct mass for the desired product. To the stirring reaction was added ~30 mL water and a few mL saline. The mixture was stirred and acidified to ~pH 1 with 1N HCl - a gelatinous precipitate formed. The mixture was stirred rapidly and diethyl ether (10 mL) was added – the precipitate became more granular and became suspended mostly in the organic layer. The quench mixture was stirred at room temperature for ~30 minutes then the solid was collected on a fritted funnel, washed well with water then diethyl ether, then dried in vacuo to yield product 60 mg (81% yield) as a white powder. LC/MS (FA) ES+ 346. ^{1}H NMR (400 MHz, DMSO) δ 13.62 – 13.20 (s, 1H), 8.63 – 8.52 (dd, J = 4.7, 1.5 Hz, 2H), 7.91 – 7.80 (m, 3H), 7.80 – 7.72 (d, J = 3.0 Hz, 2H), 7.70 – 7.63 (dd, J = 4.6, 1.5 Hz, 2H), 7.53 – 7.40 (m, 3H), 4.57 – 4.48 (s, 2H).

[00788] Example 41: Synthesis of 2-(2-acetamidopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylic acid (Compound 177)

[00789]



[00790] Step 1, Preparation of ethyl 2-(2-acetamidopyridin-4-yl)-4-bromothiazole-5-carboxylate

[00791] A mixture of ethyl 2,4-dibromothiazole-5-carboxylate (0.500 g, 1.59 mmol), N-(4-(trimethylstannyl)pyridin-2-yl)acetamide (0.569 g, 1.90 mmol), tetrakis(triphenylphosphine)palladium(0) (91.7 mg, 0.0794 mmol), copper(I) iodide (90.7 mg, 0.476 mmol), and lithium chloride (202 mg, 4.76 mmol) in dioxane (29.1 mL) was degassed with nitrogen and heated at reflux for 1 hr. The reaction was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 0/100→50/50) to give 312 mg of the title compound. (44 % yield). LC/MS (FA) ES+ 370, 372. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (s, 1H), 8.39 (d, 1H, J = 5.2 Hz), 8.25 (bs, 1H), 7.68 (dd, 1H, J = 5.2, 1.6 Hz), 4.41 (q, 2H, J = 7.2 Hz), 2.26 (s, 3H), 1.41 (t, 3H, J = 7.2 Hz).

[00792] Step 2, Preparation of ethyl 2-(2-acetamidopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylate

[00793] To a mixture of ethyl 2-(2-acetamidopyridin-4-yl)-4-bromothiazole-5-carboxylate (190 mg, 0.510 mmol) and bis(tri-t-butylphosphine)palladium(0) (65.6 mg, 0.128 mmol) under nitrogen was added a 0.500 M solution of 2-napthylmethylzinc bromide in THF (3.60 mL, 1.80 mmol). The reaction was stirred at room temperature for 5 minutes, then at 60 degrees for 1 hour. Another portion of bis(tri-t-butylphosphine)palladium(0) (60.0 mg, 0.117 mmol) was added, followed by another portion of 0.500 M solution of 2-napthylmethylzinc bromide in THF (3.00 mL, 1.50 mmol), and the reaction was heated at 60 degrees for an additional 45 minutes. The reaction was cooled to room temperature and quenched with saturated ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 0/100→100/0) to give 100 mg of the title compound. (40 % yield). LC/MS (FA) ES+ 432.

[00794] Step 3, Preparation of 2-(2-aminopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylic acid, HCl salt

[00795] To a mixture of ethyl 2-(2-acetamidopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylate (100 mg, 0.232 mmol) in THF (2.00 mL) was added 1.0 M aqueous LiOH (2.32 mL, 2.32 mmol) and the resulting mixture was heated at 40 degrees for 3 days. The mixture was acidified with 1N HCl and the resulting precipitate was filtered and dried to give the 85 mg of the crude HCl salt (100% yield) which was used as is in the next step. LC/MS (FA) ES+ 362.\

Step 4, Preparation of 2-(2-acetamidopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylic acid

a solution of (2-aminopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylic acid, HCl salt (85.0 mg, 0.214 mmol) in acetic anhydride (1.15 mL, 12.2 mmol) and pyridine (0.300 mL, 3.71 mmol) was added DMAP (0.30 mg, 0.0024 mmol) and the resulting solution was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue was purified by silica gel

chromatography (MeOH/DCM = 0/100→40/60) to give 20 mg of the title compound (23 % yield). LC/MS (FA) ES+ 404. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.84 (bs, 1H), 10.7 1 (s, 1H), 8.63 (s, 1H), 8.41 (d, 1H, J = 5.2 Hz), 7.86-7.82 (m, 3H), 7.76 (s, 1H), 7.57 (dd, 1H, J = 5.2, 1.2 Hz), 7.49-7.42 (m, 3H), 4.70 (s, 2H), 2.10 (s, 3H).

[00796] The following analytical methods were used for examples below:

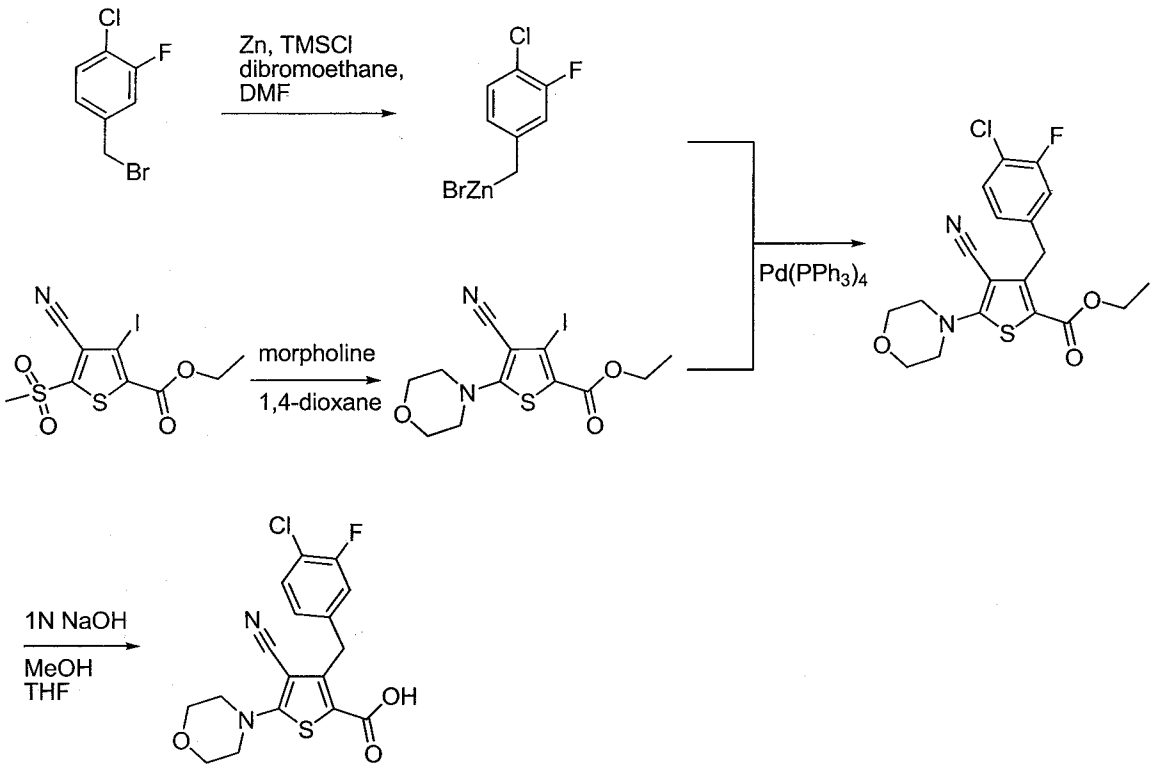
[00797] LCMS sectra were run on a Phenominex Luna 5μm C18 50 × 4.6 mm column on a Hewlett-Packard HP1100 using the following gradients:

- Method Formic Acid (FA): Acetonitrile containing 0 to 100 percent 0.1 % formic acid in water (2.5 ml/min for a 3 minute run).
- Method Ammonium Acetate (AA): Acetonitrile containing 0 to 100 percent 10 mM ammonium acetate in water (2.5 ml/min for a 3 minute run).

[00798] Chiral isomers were separated using chiral HPLC on a Chiralpak IC 250x25 mm 5 micron column using hexane/ethanol/diethylamine or hexane/isopropylalcohol/ethanol/diethylamine as mobil phase. Absolute configurations of the separated isomers were unknown, structures were assigned arbitrarily.

[00799] NMR spectrum is shown by proton NMR, with tetramethylsilane as the internal standard and using 300MHz Bruker Avance spectrometer equipped with a 5mm QNP probe and 400MHz Bruker Avance II spectrometer equipped with a 5mm QNP probe for the measurement; δ values are expressed in ppm.

[00800] Example 42: Synthesis of 3-(4-chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylic acid (Compound 94).



[00801] **Step 1:** Ethyl 4-cyano-3-iodo-5-morpholin-4-ylthiophene-2-carboxylate.

[00802] To a 500 mL RBF containing ethyl 4-cyano-3-iodo-5-(methylsulfonyl)thiophene-2-carboxylate (17.20 g, 44.65 mmol, prepared as in WO 2009154741) was added anhydrous 1,4-dioxane (172.0 mL, 2204 mmol). To the resulting suspension was added morpholine (8.177 mL, 93.77 mmol). A reflux condenser was attached and the pink/orange heterogeneous suspension was heated to bath temp 90 °C and allowed to stir. Shortly after heating began, reaction mixture became a cherry red, homogenous solution. Reaction was stirred for 16 hours at 90 °C. The reaction was then cooled to room temperature and diluted with water (100 mL). Mixture was filtered, and the solid was dried for in vacuo at 40 °C for 5 days to afford ethyl 4-cyano-3-iodo-5-morpholin-4-ylthiophene-2-carboxylate (14.3 grams, 82% yield). LCMS: (FA) ES+ 393; ^{1}H NMR (400 MHz, DMSO) δ 4.24 (q, J = 7.1, 2H), 3.78 – 3.70 (m, 4H), 3.63 – 3.57 (m, 4H), 1.26 (t, J = 7.1, 3H).

[00803] **Step 2:** Ethyl 3-(4-chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylate.

[00804] In a flame-dried scintillation vial, to a suspension of zinc (0.0998 g, 1.53 mmol) in N,N-dimethylformamide (1.36 mL, 17.6 mmol) were added 1,2-dibromoethane (0.003279 mL, 0.03805 mmol) and chlorotrimethylsilane (0.004830 mL, 0.03805 mmol). Stirred at room temperature for 15 min, at

which point a solution of 3-fluoro-4-chlorobenzylbromide (0.341 g, 1.53 mmol) in N,N-dimethylformamide (1.36 mL, 17.6 mmol) was added. The resulting suspension was stirred at room temperature for 16 hours. A scintillation vial containing ethyl 4-cyano-3-iodo-5-morpholin-4-ylthiophene-2-carboxylate (199 mg, 0.507 mmol and bis(tri-t-butylphosphine)palladium(0) (12.96 mg, 0.02537 mmol) was purged via vacuum/backfilling with argon. To this was added the organozinc solution from above, and the resulting solution was stirred at 45 °C for 6 hours, at which point LC/MS showed complete conversion to a single new peak with mass representing desired product. The reaction mixture was transferred to a separatory funnel containing saturated $NaHCO_3$ (aq., 10 mL) and water (10 mL), and then diluted with EtOAc (40 mL). The layers were separated, and the aqueous layer was extracted 2 x 30 mL with EtOAc. The combined organic layers were washed 1 x brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford crude ethyl 3-(4-chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylate as a brown oil that was used without further purification. LCMS: (FA) ES+ 409, 411

[00805] **Step 3:** 3-(4-Chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylic acid (Compound **94**).

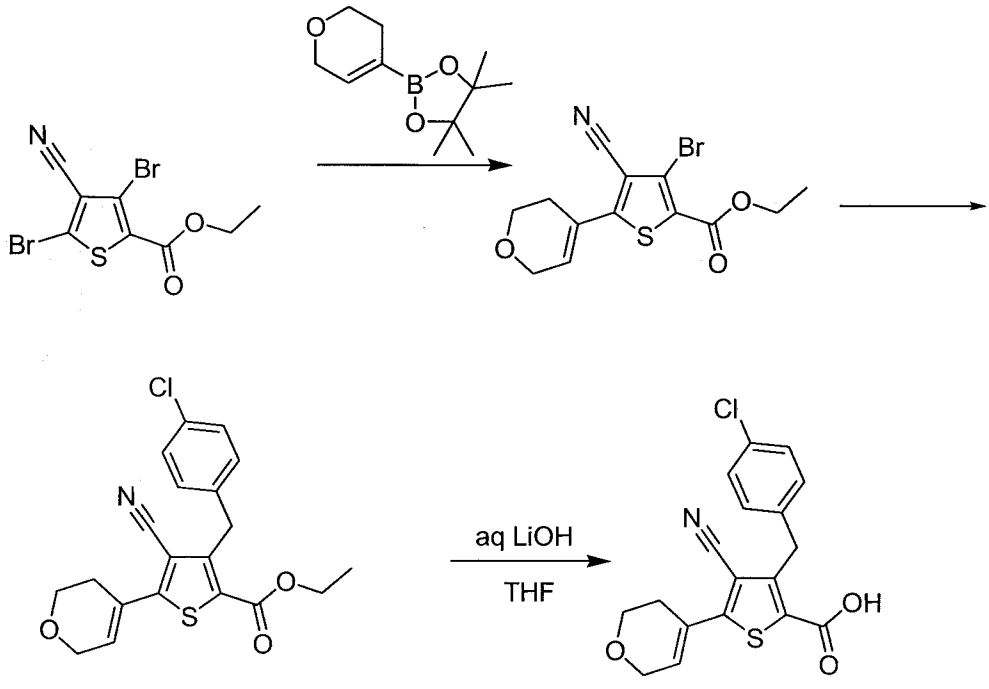
[00806] To a solution of ethyl 3-(4-chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylate in tetrahydrofuran (5.64 mL, 69.6 mmol) was added methanol (2.5 mL, 62 mmol) and 1 M sodium hydroxide in water (4.23 mL, 4.23 mmol) and the resulting suspension was stirred at room temp. The reaction was stirred for 16 hours at room temperature. Volatiles were then removed in vacuo, and the residue diluted with EtOAc (30 mL). Mixture was then transferred to a separatory funnel containing 1N HCl (5.0 mL) and water (10 mL), at which time the pH of aqueous layer was measured at ~2.0. Layers were separated, and the aqueous layer was extracted 3 x 20 mL with EtOAc. Combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo. Resulting residue was adsorbed to celite, and the resulting solid was placed into a dryload cartridge and purified via column chromatography (gradient elution, 0-5% MeOH:CH_2Cl_2) to afford 3-(4-chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylic acid (**94**) as a white solid (0.128 g, yield 66.3%). LCMS: (FA) ES+ 381, 383; ^{1}H NMR (400 MHz, DMSO) δ 13.25 (s, 1H), 7.52 (dd, J = 8.1, 8.1, 1H), 7.22 (dd, J = 1.9, 10.5, 1H), 7.05 (dd, J = 1.5, 8.3, 1H), 4.31 (s, 2H), 3.80 – 3.65 (dd, J = 4.5, 5.2, 4H), 3.59 – 3.47 (dd, J = 4.5, 5.2, 4H).

[00807] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 42.

96	LC/MS: (FA) ES- 395, 397

97	LC/MS: (AA) ES+ 347
102	LC/MS: (FA) ES- 411
105	LC/MS: (AA) ES+ 359
106	LC/MS: (FA) ES- 405, 407
107	LC/MS: (FA) ES- 381
108	LC/MS: (FA) ES+ 393, 395
112	LC/MS: (FA) ES+ 379
115	LC/MS: (FA) ES+ 354
116	LC/MS: (FA) ES+ 363
117	LC/MS: (FA) ES- 391, 393
122	LC/MS: (FA) ES- 391, 393
123	LC/MS: (FA) ES+ 381
124	LC/MS: (FA) ES- 395, 397
125	LC/MS: (FA) ES+ 393, 395
126	LC/MS: (FA) ES- 397, 399
127	LC/MS: (FA) ES- 409, 411
300	LC/MS: (FA) ES- 397

[00808] Example 43: Synthesis of 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylic acid (Compound 95).



[00809] **Step 1:** Ethyl-3-bromo-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate.

[00810] To a microwave vial containing a suspension of ethyl 3,5-dibromo-4-cyanothiophene-2-carboxylate (300.0 mg, 0.8849 mmol, prepared as in MPI10-008P1M) and 3,6-dihydro-2h-pyran-4-boronic acid pinacol ester (204 mg, 0.973 mmol) in 1,4-dioxane (8.98 mL, 115 mmol) and water (0.925 mL, 51.3 mmol) were added tetrakis(triphenylphosphine)palladium(0) (102 mg, 0.0885 mmol) and cesium carbonate (865 mg, 2.65 mmol). The vial was sealed, degassed by bubbling argon through for 10 minutes, and then heated at 100 °C with stirring for 24 h. The reaction was then cooled to room temperature and partitioned between EtOAc and water. Layers were separated, and the aqueous layer was extracted 2x with EtOAc. Combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Residue was subjected to column chromatography as a solution in DCM (40 g column, gradient elution 0 to 25% EtOAc/hexanes) to afford ethyl 3-bromo-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate as a white solid (183 mg, yield 63%). LCMS: (FA) ES+ 342, 344; ^{1}H NMR (400 MHz, DMSO) δ 6.86 – 6.79 (m, 1H), 4.36 – 4.27 (m, 4H), 3.82 (dd, J = 5.4, 5.4, 2H), 2.53 (ddd, J = 2.1, 4.9, 10.0, 2H), 1.30 (dd, J = 7.1, 7.1, 3H).

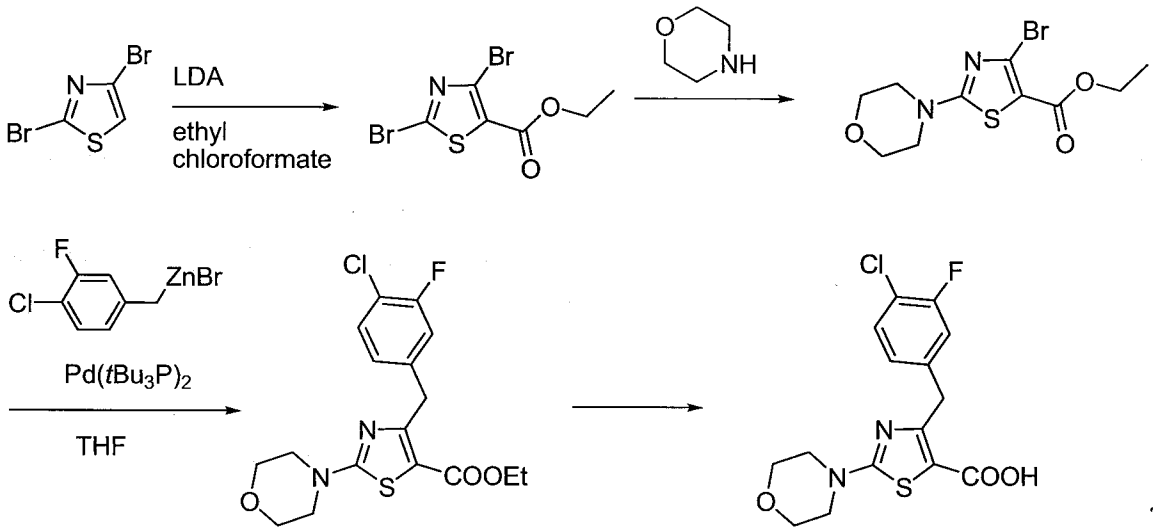
[00811] **Step 2:** Ethyl 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate.

[00812] In a sealable reaction vial, ethyl 3-bromo-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate (180.0 mg, 0.5260 mmol) and a stir pea were azeotroped with toluene 3x and dried under high vacuum overnight. To the vial was added bis(tri-t-butylphosphine)palladium(0) (26.88 mg, 0.05260 mmol). Vial was evacuated and then back-filled with argon 2X, at which time was added via syringe 4-chlorobenzylzinc chloride as a 0.50 M solution in tetrahydrofuran (3.682 mL, 1.841 mmol). The reaction was heated with stirring at 60° C for 2h. Reaction was cooled to room temperature and then diluted with EtOAc and sat. aq. NH_4Cl. Mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer extracted 2x with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered through a pad of Celite, and concentrated in vacuo to afford a yellow oil. The residue was dissolved in DCM and loaded onto 40 g ISCO column (gradient elution: 0-25% EtOAc/hexanes) to afford ethyl 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate (92 mg, 43.6%) as a yellow solid. LC/MS: (AA) ES- 386, 388; ^{1}H NMR (400 MHz, DMSO) δ 7.38 – 7.33 (m, 2H), 7.22 (m, 2H), 6.80 – 6.76 (m, 1H), 4.40 (s, 2H), 4.34 – 4.24 (m, 4H), 3.80 (dd, J = 5.4, 5.4, 2H), 2.52 (dd, J = 2.2, 5.0, 2H), 1.26 (dd, J = 7.1, 7.1, 3H).

[00813] **Step 3:** 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylic acid (Compound **95**).

[00814] To a round bottom flask containing ethyl 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate (43.0 mg, 0.111 mmol) were added tetrahydrofuran (1.23 mL, 15.2 mmol), sodium hydroxide (1.0N in water, 0.925 mL, 0.925 mmol), and methanol (0.617 mL, 15.2 mmol). The mixture was stirred at room temperature overnight. Reaction was quenched via addition of 1N HCl in water (2 mL), then diluted with EtOAc and transferred to separatory funnel. The layers were separated, and the aqueous layer was extracted 2x with EtOAc. Combined organics were washed with brine, dried over Na_2SO_4, and filtered, at adsorbed to Celite (10 mL). Column chromatography (40 g ISCO column, gradient elution 0-8% MeOH/DCM afforded 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylic acid (**95**) (25 mg, 63%) as a white solid. LC/MS: (FA) ES- 358, 360; ^{1}H NMR (400 MHz, DMSO) δ 14.04 (br s, 1H), 7.33 (d, J = 8.5, 2H), 7.26 (d, J = 8.5, 2H), 6.64 (s, 1H), 4.43 (s, 2H), 4.24 (d, J = 2.9, 2H), 3.79 (dd, J = 5.4, 5.4, 2H), 3.32 (br s, 2H).

[00815] **Example 44: Synthesis of 4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylic acid (Compound 118).**



[00816] **Step 1:** Ethyl 2,4-dibromo-1,3-thiazole-5-carboxylate.

[00817] In a 50mL 2-neck RBF equipped with septa, a solution of N,N-Diisopropylamine (0.04374 g, 0.4322 mmol) in tetrahydrofuran (1.33 mL, 16.4 mmol) under atmosphere of argon was cooled at -78 °C, at which point n-butyllithium (2.50 M in hexane, 0.1647 mL, 0.4116 mmol) was added dropwise and the resulting solution was stirred for 30 minutes at -78 °C. To the above solution was added dropwise a solution of 2,4-dibromothiazole (0.100 g, 0.412 mmol) in tetrahydrofuran (1.33 mL, 16.4 mmol) at -78

°C, and this solution was stirred for 30 min -78 °C . Next, ethyl chloroformate (0.07872 mL, 0.8233 mmol) was added dropwise at -78 °C and the mixture was stirred for 30 minutes. The reaction was quenched by addition of water (20 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via silica gel column chromatography (12g Analogix column, gradient elution 5% to 10% EtOAc in hexane) to afford ethyl 2,4-dibromo-1,3-thiazole-5-carboxylate (60 mg, yield 46%). LC/MS: (FA) ES+ 314, 316, 318; ^{1}H NMR (400 MHz, CDCl3) δ 4.37 (q, J = 7.1, 2H), 1.44 – 1.33 (m, 3H).

[00818] **Step 2:** Ethyl 4-bromo-2-morpholin-4-yl-1,3-thiazole-5-carboxylate.

[00819] In a sealable reaction vessel, to a suspension of ethyl 2,4-dibromo-1,3-thiazole-5-carboxylate (2.90 g, 9.21 mmol, prepared as in WO 2005026149) and cesium carbonate (9.00 g, 27.6 mmol) in tetrahydrofuran (24.3 mL, 299 mmol) was added morpholine (0.883 mL, 10.1 mmol), at which point the vessel was sealed and the mixture was heated with stirring at 90 °C for 4 hours. Reaction mixture was diluted with EtOAc and water and transferred to a separatory funnel. Layers were separated, and the organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. Residue was subjected to column chromatography (gradient elution, 0 to 50% EA in hexanes) to afford ethyl 4-bromo-2-morpholin-4-yl-1,3-thiazole-5-carboxylate (2.4 g, yield 81%) as a white solid. LC/MS: (FA) ES+ 321, 323; ^{1}H NMR (300 MHz, CDCl3) δ 4.30 (dd, J = 7.1, 7.1, 2H), 3.82 – 3.75 (m, 4H), 3.58 – 3.50 (m, 4H), 1.34 (dd, J = 7.1, 7.1, 3H).

[00820] **Step 3:** Ethyl-4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylate.

[00821] In a 50ml flame-dried round bottom flask, a suspension of zinc (0.183 g, 0.00280 mol), chlorotrimethylsilane (8.9 uL, 0.000070 mol) and 1,2-dibromoethane (6.0 uL, 0.000070 mol) in N,N-dimethylformamide (2.4 mL, 0.031 mol) was stirred for 15 minutes. To this was added a solution of 3-fluoro-4-chlorobenzylbromide (0.626 g, 0.00280 mol) in N,N-dimethylformamide (4.8 mL, 0.062 mol), and the resulting suspension was stirred overnight at room temperature. To a flame-dried 50 ml round bottom flask containing ethyl 4-bromo-2-morpholin-4-yl-1,3-thiazole-5-carboxylate (0.300 g, 0.000934 mol) and bis(tri-t-butylphosphine)palladium(0) (36 mg, 0.000070 mol) was added the organozinc solution from above, and the reaction was heated with stirring at 60 °C for 60 min. Reaction was quenched with saturated ammonium chloride, and then transferred to a separatory funnel containing water (10 mL) and EtOAc (40 mL). The layers were separated, and the aqueous layer was extracted 2 x 30 mL with EtOAc. The combined organic layers were washed 1 x brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was dissolved in DCM, adsorbed onto silica gel and purified via column

chromotography (24 gram Isco column, gradient elution, 0-50% EtOAc / hexanes) to afford ethyl 4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylate (245 mg, yield 68.2%).

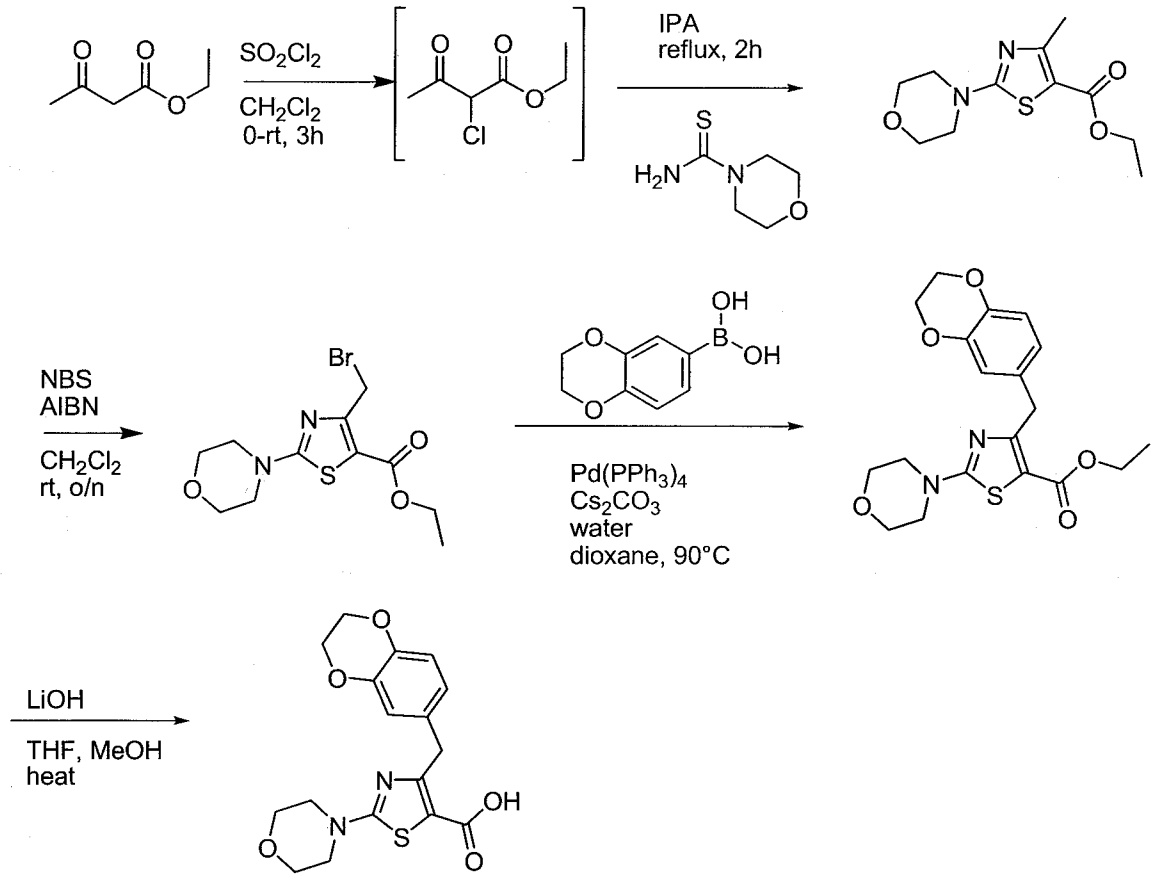
[00822] **Step 4:** 4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylic acid (Compound **118**).

[00823] In a 50 mL round bottom flask were combined ethyl 4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylate (0.245 g, 0.000637 mol), tetrahydrofuran (5.49 mL, 0.0677 mol) and a solution of lithium hydroxide (2.0 M in water, 3.18 mL, 0.00637 mol). The mixture was heated at 80 °C with stirring for 2 days, and then cooled to room temperature and diluted with water. Reaction mixture was then carefully adjusted to pH 5 via addition of 1N HCl and transferred to a separatory funnel containing EtOAc (40 mL). Layers were separated, and the aqueous layer was extracted 2 x 30 mL with EtOAc. The combined organic layers were washed 1 x brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a white solid, which was dissolved in DCM and adsorbed onto silica gel. Column chromatography (4 g column, gradient elution 0-20% MeOH in DCM) then afforded 4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylic acid (**118**) (31 mg, 14%). LC/MS: (FA) ES+ 357, 359; ^{1}H NMR (400 MHz, DMSO) δ 12.79 (s, 1H), 7.48 (t, J = 8.1, 1H), 7.24 (dd, J = 1.9, 10.5, 1H), 7.08 (dd, J = 1.5, 8.3, 1H), 4.24 (s, 2H), 3.71 – 3.62 (m, 4H), 3.46 – 3.38 (m, 4H).

[00824] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 44

91	LC/MS: (FA) ES+ 339
93	LC/MS: (FA) ES+ 330
98	LC/MS: (FA) ES+ 355
101	LC/MS: (FA) ES+ 357, 359
103	LC/MS: (FA) ES+ 335
104	LC/MS: (FA) ES+ 373, 375, 377
109	LC/MS: (FA) ES+ 389
111	LC/MS: (FA) ES+ 373
114	LC/MS: (FA) ES+ 373, 375, 377
119	LC/MS: (FA) ES+ 323
120	LC/MS: (FA) ES+ 369, 371

[00825] Example 45: Synthesis of 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (Compound 110).



[00826] **Step 1**: Butanoic acid, 2-chloro-3-oxo-, ethyl ester.

[00827] In a 500 mL round bottomed flask, to a solution of 3-oxobutanoic acid ethyl ester (7.69 mL, 60.3 mmol) in methylene chloride (150 mL, 2300 mmol) at 0 °C was slowly added sulfuryl chloride (6.30 mL, 77.8 mmol). The mixture was stirred for 3 hours, and then quenched with saturated $NaHCO_3$. Mixture was transferred to a separatory funnel the layers were separated. The organic layer was washed 1 x brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford butanoic acid, 2-chloro-3-oxo-, ethyl ester which was immediately used without further purification.

[00828] **Step 2:** Ethyl 4-methyl-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate.

[00829] In a 100 mL round bottomed flask, to a solution of butanoic acid, 2-chloro-3-oxo-, ethyl ester (11.2 g, 68.4 mmol) in isopropyl alcohol (250 mL, 3300 mmol) was added morpholine-4-carbothioicacidamide (10.0 g, 68.4 mmol). The mixture was stirred at reflux for 1 hour, and then stirred at room temperature for 3 days. Volatiles were removed in vacuo, and the resulting residue was dissolved in ethyl acetate and diluted with saturated, aqueous sodium bicarbonate. The mixture was transferred to a

separatory funnel, the layers were separated, and the organic layer dried with Na2SO4, filtered and concentrated in vacuo. The crude product was dissolved in DCM, adsorbed onto silica gel, and purified via column chromatography (120 g Isco column, gradient elution, 0-100% EtOAc/hexanes) to afford ethyl 4-methyl-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (14.51 g, yield for 2 steps, 82%). LC/MS: (FA) ES+ 257, 259; ^{1}H NMR (400 MHz, CDCl3) δ 4.26 (dd, J = 7.1, 7.1, 2H), 3.87 – 3.67 (m, 4H), 3.59 – 3.42 (m, 4H), 2.55 (s, 3H), 1.33 (dd, J = 7.1, 7.1, 3H).

[00830] **Step 3:** Ethyl 4-(bromomethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate.

[00831] To a round bottom flask containing a solution of ethyl-4-methyl-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (14.50 g, 56.57 mmol) in methylene chloride (400 mL, 6000 mmol) were added N-bromosuccinimide (10.07 g, 56.57 mmol) and 2,2'-azo-bis-isobutyronitrile (464 mg, 2.83 mmol). The mixture was stirred at reflux overnight. Reaction was quenched via addition of 10% aqueous sodium bisulfite (20 g in 200 ml water) and stirred for 20 minutes. Mixture was transferred to a separatory funnel, the layers separated, and the aqueous layer was extracted 2 x DCM. Combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was dissolved in DCM and adsorbed onto silica gel. Purification via column chromatography (220 g Isco column, gradient elution 0-10% EtOAc in 1:1 DCM:hexanes) afforded ethyl 4-(bromomethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (13.5 g, yield 71.1%). LC/MS: (FA) ES+ 335, 337; ^{1}H NMR (300 MHz, CDCl3) δ 4.76 (s, 2H), 4.30 (dd, J = 7.1, 7.1, 2H), 3.88 – 3.72 (m, 4H), 3.62 – 3.49 (m, 4H), 1.35 (dd, J = 7.1, 7.1, 3H).

[00832] **Step 4:** Ethyl 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate.

[00833] Ethyl 4-(bromomethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (109.4 mg, 0.326 mmol), 1,4-benzodioxane-6-boronic acid (91.0 mg, 0.506 mmol), tetrakis(triphenylphosphine)palladium(0) (43.0 mg, 0.0372 mmol), cesium carbonate (430 mg, 1.3 mmol), 1,4-dioxane (2.19 mL, 28.0 mmol) and water (43.8 uL, 2.43 mmol) were combined in a vial equipped with a stirbar. The vial was sealed and the atmosphere was replaced with nitrogen. The vial was sonicated for 1 minute then heated at 90°C (heating block temperature) with stirring for 1 hour. The reaction was cooled to room temperature, the vial was opened and the contents were quenched into stirring saline. The quench mixture was transferred to a separatory funnel and extracted twice with ethyl acetate. The extracts were combined, washed with saline, dried over sodium sulfate, filtered, and concentrated in vacuo to leave an orange oil. The crude residue was purified by silica gel chromatography (gradient elution: ethyl acetate/hexane from 0/100 to 100/0) to give ethyl 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (60 mg, 47% yield)

as a white powder. LC/MS (FA) ES+ 391; ^{1}H NMR (300 MHz, DMSO-d6) δ: 6.67-6.74 (m, 3H), 4.20 (q, 2H, J = 7.1 Hz), 4.17 (s, 4H), 4.07 (s, 2H), 3.69-3.65 (m, 4H), 3.46-3.43 (m, 4H), 1.24 (t, 3H, J = 7.1 Hz).

[00834] **Step 5:** 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (Compound **110**).

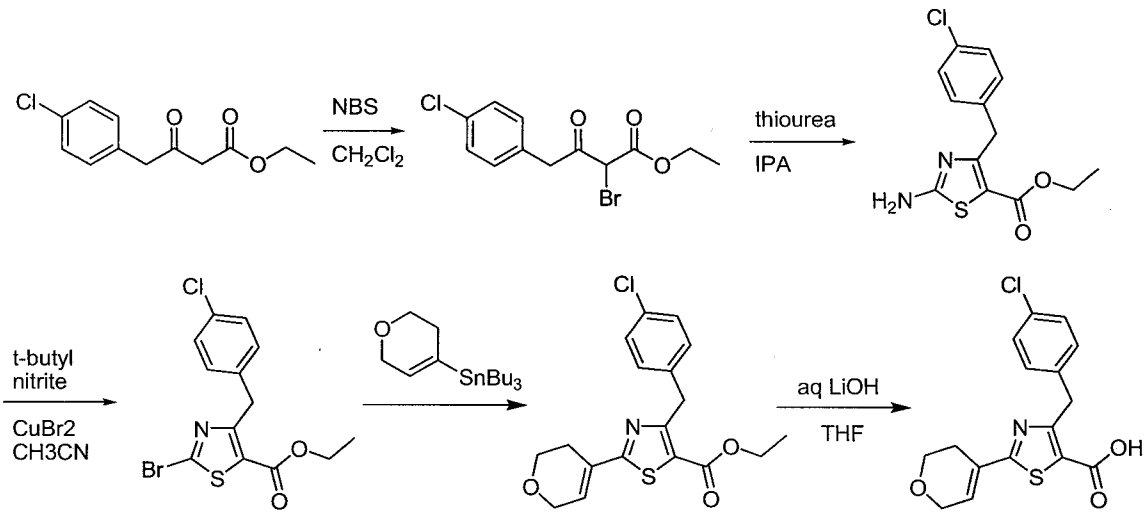
[00835] Ethyl 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (58.0 mg, 0.000148 mol) was placed in a 50 ml round bottom flask equipped with a stirbar. Tetrahydrofuran (2.25 mL, 0.0277 mol) and methanol (0.50 mL, 0.012 mol) were added and the mixture was stirred to give a clear solution. A solution of lithium hydroxide in water (2.0M, 0.750 mL, 0.00150 mol) was added in a single portion, resulting in a pale yellow solution which was stirred at room temperature under an atmosphere of nitrogen for 15 minutes. The reaction was then heated at reflux for 2.5 hours, cooled to rt, and diluted with water (~25 ml) to give a clear slightly gray solution, which was allowed to stir at room temperature overnight under an atmosphere of nitrogen. 1 N HCl (~1.8ml) was slowly added to the stirring solution to lower the pH to ~3 (pH paper) whereupon a white precipitate formed. The mixture was stirred for ~15 minutes, at which point the solid was collected on a fritted funnel, washed with water, and dried on the funnel with house vacuum under a stream of nitrogen for several hours to yield 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (**110**) (45 mg, 84% yield) as a slightly gray powder. LC/MS (FA) ES+ 363; ^{1}H NMR (300 MHz, DMSO) δ 12.65 (s, 1H), 6.76 – 6.64 (m, 3H), 4.17 (s, 4H), 4.08 (s, 2H), 3.77 – 3.61 (m, 4H), 3.51 – 3.34 (m, 4H).

[00836] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 45.

99	LC/MS: (FA) ES+ 357, 359
128	LC/MS: (AA) ES+ 373
286	LC/MS: (FA) ES+ 361
288	LC/MS: (AA) ES+ 385
289	LC/MS: (FA) ES+ 376
290	LC/MS: (FA) ES+ 391, 393, 395
292	LC/MS: (AA) ES+ 356
299	LC/MS: (AA) ES+ 373
302	LC/MS: (FA) ES+ 358

303	LC/MS: (FA) ES+ 439, 441
310	LC/MS: (AA) ES+ 373
314	LC/MS: (AA) ES+ 373
318	LC/MS: (FA) ES+ 398
319	LC/MS: (AA) ES+ 373
325	LC/MS: (FA) ES+ 380
328	LC/MS: (FA) ES+ 344
335	LC/MS: (AA) ES+ 385
338	LC/MS: (AA) ES+ 373
339	LC/MS: (FA) ES+ 365
340	LC/MS: (AA) ES+ 373
341	LC/MS: (AA) ES+ 345
344	LC/MS: (AA) ES+ 356

[00837] Example 46: Synthesis of 4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylic acid (Compound 100).



[00838] Step 1: Ethyl 2-bromo-4-(4-chlorophenyl)-3-oxobutanoate.

[00839] In a 250 mL round bottomed flask, to a solution of ethyl 4-(4-chlorophenyl)-3-oxobutanoate (4.04 g, 16.8 mmol) in methylene chloride (100 mL, 2000 mmol) was added N-bromosuccinimide (3.13 g, 17.6 mmol) and the mixture was stirred for 3 h at room temperature. Reaction was quenched via addition of a 10% aqueous solution of $NaHSO_3$ (50 mL), and the resulting biphasic mixture was vigorously stirred for 15 minutes. The reaction mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers

were washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford ethyl 2-bromo-4-(4-chlorophenyl)-3-oxobutanoate (5.23 g, yield 97.5%) as a yellow oil that was used without further purification. LC/MS (FA) ES- 317, 319, 321.

[00840] **Step 2:** Ethyl 2-amino-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate.

[00841] In a 100 mL round bottomed flask, to a solution of ethyl 2-bromo-4-(4-chlorophenyl)-3-oxobutanoate (990 mg, 3.1 mmol) in isopropyl alcohol (20 mL, 300 mmol) was added thiourea (590 mg, 7.8 mmol) and the resulting mixture was stirred at reflux for 16 hours. The mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was suspended in EtOAc (50 mL) and then washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), brine (50 mL). The resulting organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to afford ethyl 2-amino-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (900 mg, yield >99%) as a yellowish solid that was used without further purification. LC/MS (FA) ES+ 297, 299.

[00842] **Step 3:** Ethyl 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate.

[00843] In a 250 mL round bottomed flask, to a solution of ethyl 2-amino-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (786 mg, 2.65 mmol) in acetonitrile (75 mL, 1400 mmol) was added copper(II) bromide (963 mg, 4.31 mmol). The suspension was stirred at room temperature for 15 minutes to afford a green solution. To the mixture was added tert-butyl nitrite (0.630 mL, 5.30 mmol) and the reaction was then heated with stirring at 70 °C for 1.5 hours. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by column chromatography (80 gram column, gradient elution 10% to 50% EtOAc/hexanes) to afford ethyl 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (820 mg; yield 86%) as a yellow syrup. LC/MS (FA) ES+ 360, 362, 364; ^{1}H NMR (400 MHz, CDCl3) δ 7.33 – 7.20 (m, 4H), 4.44 (s, 2H), 4.34 (dd, J = 7.1, 7.1, 2H), 1.36 (dd, J = 7.1, 7.1, 3H).

[00844] **Step 4:** Ethyl-4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylate.

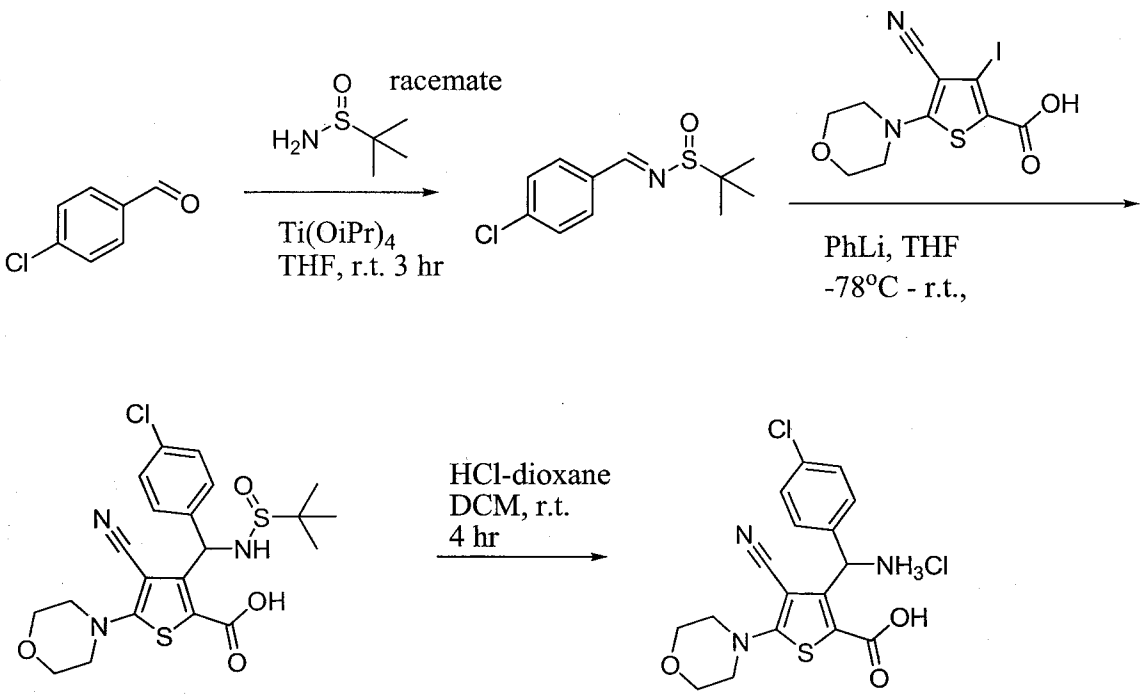
[00845] A mixture of ethyl 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (289 mg, 0.802 mmol), tributyl(3,6-dihydro-2H-pyran-4-yl)stannane (332 mg, 0.890 mmol), tetrakis(triphenylphosphine)palladium(0) (46.4 mg, 0.0401 mmol), lithium chloride (1.20E2 mg, 2.82 mmol) and copper(I) iodide (45.8 mg, 0.241 mmol) in dry 1,4-dioxane (6.26 mL, 80.2 mmol) was degassed by vacuum and backfilling with argon four times, and then heated under argon at reflux for 3 hours. The mixture was filtered thru Celite, washing with 10% MeOH in DCM. Volatiles were removed in vacuo, and the residue was adsorbed to silica gel by concentrating a DCM solution to which silica gel

had been added. Column chromatography (gradient elution, 0 to 20% EA in hexanes) afforded ethyl-4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylate (113 mg, 38.9%) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ 7.35 - 7.31 (m, 2H), 7.27 - 7.23 (m, 2H), 6.86 - 6.83 (m, 1H), 4.40 (s, 2H), 4.29 (q, J = 6.9, 2H), 4.25 – 4.22 (m, 2H), 3.78 (t, J = 5.4, 2H), 2.51 – 2.46 (m, 2H), 1.27 (t, J = 6.9 Hz, 3H).

[00846] **Step 5:** 4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylic acid (Compound **100**).

[00847] In a round bottom flask equipped with a stir bar, a solution of ethyl 4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylate (109 mg, 0.300 mmol) in tetrahydrofuran (3.33 mL, 41.1 mmol) and methanol (1.67 mL, 41.1 mmol) was treated with lithium hydroxide (1.0M in water, 2.40 mL, 2.40 mmol). The mixture was stirred at room temperature overnight. pH was adjusted to ~3 via addition of 1N aqueous HCl solution, and the reaction was then diluted with EtOAc and transferred to separatory funnel. The layers were separated, and the aqueous layer was extracted 2x with EtOAc. Combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (gradient elution, 0 to 10 % MeOH in DCM) afforded 4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylic acid (**100**) (53 mg, yield 53% as a white powder. LCMS: (FA) ES+ 336; ^{1}H NMR (400 MHz, DMSO) δ 13.52 (bs, 1H), 7.35 – 7.31 (m, 2H), 7.27-7.23 (m, 2H), 6.82 – 6.79 (m, 1H), 4.40 (s, 2H), 4.24 – 4.22 (m, 2H), 3.77 (t, J = 5.4, 2H), 2.50 – 2.45 (m, 2H).

[00848] **Example 47: Synthesis of 3-[amino(4-chlorophenyl) methyl]-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylic acid hydrochloride (Compound 113).**



[00849] **Step 1:** N-[(E)-(4-chlorophenyl)methylene]-2-methylpropane-2-sulfinamide.

[00850] To a solution of 4-chlorobenzaldehyde (2.88 g, 20.5 mmol), (S)-(-)-2-methyl-2-propanesulfinamide (1.40 g, 11.6 mmol), and (R)-(+)-2-methyl-2-propanesulfinamide (1.40 g, 11.6 mmol) in anhydrous tetrahydrofuran (30.0 mL) under nitrogen atmosphere was added titanium tetraisopropoxide (6.00 mL, 20.3 mmol) dropwise. The clear solution was stirred at room temperature for 3 hours. Methylene chloride (200 mL) and water (2.0 mL) were added and the mixture was stirred at room temperature for 1 hour. The suspension was filtered through Celite and washed with DCM. The filtrate was concentrated in vacuo and purified by column chromatography (gradient elution: 0-20% EtOAc/hexane) to afford N-[(E)-(4-chlorophenyl)methylene]-2-methylpropane-2-sulfinamide (3.93 g, yield 78.7%). LCMS: (FA) ES+ 244; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.78-7.80 (d, 2H, J = 8.53 Hz), 7.44-7.47(d, 2H, J = 8.53 Hz), 1.26 (s, 9H).

[00851] **Step 2:** 3-{[(tert-butylsulfinyl)amino](4-chlorophenyl)methyl}-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylic acid.

[00852] 4-cyano-3-iodo-5-morpholin-4-ylthiophene-2-carboxylic acid (1.44 g, 3.96 mmol, prepared as in WO2009/154741) was suspended in anhydrous tetrahydrofuran (80.0 mL, 986 mmol), sonicated under nitrogen atmosphere for 10 min, and cooled in an acetone-dry ice bath for 10 minutes. Phenyllithium (1.8M in n-butyl ether, 8.81 mL, 15.9 mmol) was added dropwise over 7 minutes. The suspension was stirred with cooling for 5 minutes, at which point the cooling bath was removed and the

suspension was stirred without cooling for 7 minutes. Reaction mixture was recooled in an acetone-dry ice bath for 10 minutes, at which point a solution of N-[(E)-(4-chlorophenyl)methylene]-2-methylpropane-2-sulfinamide (2.91 g, 11.9 mmol) in anhydrous tetrahydrofuran (20.0 mL, 246 mmol) was added dropwise over 8 minutes, and the mixture was stirred with cooling for 30 minutes. The mixture was quenched with methanol (5.0 mL, 120 mmol) and then acetic acid (1.0 mL, 18 mmol), and allowed to warm to room temperature. The volatiles were removed in vacuo, and the residue was diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with 2 x EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification via column chromatography (gradient elution: AcOH/MeOH/DCM, 0/0/100 to 0.5/4.5/95) afforded 3-{[(tert-butylsulfinyl)amino](4-chlorophenyl)methyl}-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylic acid as a mixture of diastereomers. Major diastereomer: 1.19 g, yield 62.2%. (FA) ES+ 482; ES- 480; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.33 (m, 2H), 7.15-7.17(m, 2H), 6.14 (br s, 2H), 3.87-3.89 (m, 4H), 3.60-3.63 (m, 4H), 1.21 (s, 9H). Minor diastereomer: (0.292 g, yield 15.3%). (FA) ES+ 482; ES- 480; ^{1}H NMR (400 MHz, CDCl3) δ 7.26-7.34 (m, 4H), 6.29-6.38 (m, br, 2H), 3.84-3.86 (m, 4H), 3.56-3.60 (m, 4H), 1.35 (s, 9H).

[00853] **Step 3:** 3-[amino(4-chlorophenyl) methyl]-4-cyano-5-(morpholin-4- yl)thiophene-2-carboxylic acid hydrochloride (Compound **113**).

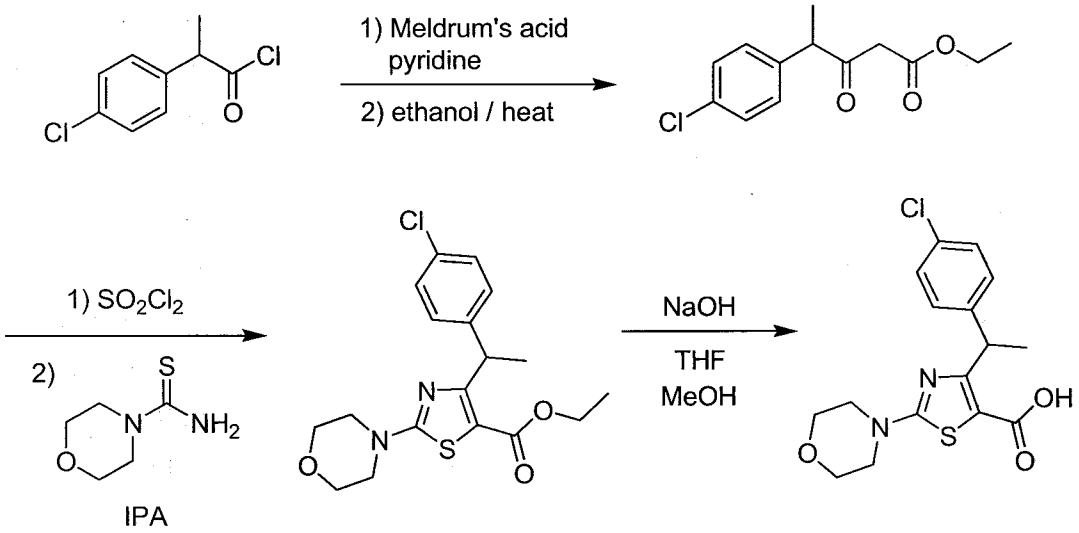
[00854] To a solution of 3-{[(tert-butylsulfinyl)amino](4-chlorophenyl)methyl}-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylic acid (1.46 g, 3.03 mmol) in methylene chloride (25.0 mL) was slowly added hydrochloric acid (4M in 1,4-dioxane, 15.0 mL), and the resultant suspension was stirred at room temperature for 1 hour. The suspension was filtered through a fine frit funnel. The collected solid was washed with DCM and dried in vacuo to afford 3-[amino(4-chlorophenyl) methyl]-4-cyano-5-(morpholin-4- yl)thiophene-2-carboxylic acid hydrochloride (**113**) (1.10 g, yield 86.5%) as a white powder . LCMS: (FA) ES+ 378; ES- 376; ^{1}H NMR (400 MHz, CD3OD) δ 7.44-7.90 (m, 4H), 5.84 (s, 1H), 3.81-3.84 (m, 4H), 3.64-3.67 (m, 4H).

[00855] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 47.

291	LC/MS: (FA) ES+ 412, 413; ES- 410, 412
317	LC/MS: (FA) ES- 454, 456
323	LCMS: (FA) ES+ 498; ES- 496
342	LC/MS: (FA) ES+ 516, 518; ES- 514, 516
353	LC/MS: (FA) ES+ 420

354	LC/MS: (FA) ES+ 452
357	LC/MS: (FA) ES+ 394; ES- 392

[00856] Example 48: Synthesis of 4-[1-(4-chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (Compound 121).



[00857] Step 1: Ethyl 4-(4-chlorophenyl)-3-oxopentanoate.

[00858] In a round bottomed flask, to a suspension of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid, 2.91 g, 20.2 mmol) in methylene chloride (11.3 mL, 177 mmol) at -10 °C (internal temp) was added pyridine (4.00 mL, 49.5 mmol) over 10 minutes. To the resulting clear solution at -10 °C, was added dropwise a solution of 2-(4-chlorophenyl)propanoyl chloride (4.10 g, 20.2 mmol) in methylene chloride (7.93 mL, 124 mmol) over 1 h. The reaction mixture was then stirred for 1h at -10 °C, and then for 1 hour at room temperature. The mixture was poured into hydrochloric acid (2.00M in water, 45.3 mL, 90.6 mmol) and ice, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with 1N HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. To the crude residue was added ethanol (39.6 mL, 679 mmol) and the mixture was heated at reflux (89 degree bath temp) for 3 hours. After cooling to room temp, the volatiles were removed in vacuo. Residue was adsorbed onto silica using DCM and purified via column chromatography (gradient elution: 0 to 20% EtOAc/hexanes to afford ethyl 4-(4-chlorophenyl)-3-oxopentanoate (2.94g, 92%) as a yellow oil. LCMS: (FA) ES+ 255; ^{1}H NMR (400 MHz, DMSO) δ 7.34 - 7.30 (m, 2H), 7.17 – 7.13 (m, 2H), 4.16 – 4.09 (m, 2H), 3.90 (q, J = 7.2, 1H), 3.40 (d, J = 15.6, 1H), 3.30 (d, J = 15.6, 1H), 1.40 (d, J = 6.8, 3H), 1.23 (t, J = 7.2, 3H).

[00859] Step 2: Ethyl 4-[1-(4-chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate.

[00860] To a solution of ethyl 4-(4-chlorophenyl)-3-oxopentanoate (1.78 g, 6.99 mmol) in methylene chloride (22.4 mL, 349 mmol) at 0 °C was added sulfuryl chloride (566 uL, 6.99 mmol) and the mixture was stirred overnight at room temperature. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and transferred to a separatory funnel. The layers were separated and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was used immediately without further purification.

In a round bottomed flask, to a solution of the crude residue from above in isopropyl alcohol (50.3 mL, 657 mmol) was added morpholine-4-carbothioicacidamide (1.44 g, 9.86 mmol). The reaction mixture was heated with stirring at 90 °C for 90 minutes. Volatiles were removed in vacuo and the residue was redissolved in DCM and treated with saturated aqueous $NaHCO_3$ with stirring for 30 minutes. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Mg_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (gradient elution: 0 to 25% EtOAc in hexanes) afforded ethyl 4-[1-(4-chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (1.45 g, 57.9%) as a white solid. LCMS: (FA) ES+ 381; ^{1}H NMR (400 MHz, DMSO) δ 7.41 – 7.37 (m, 2H), 7.24 – 7.21 (m, 2H), 5.12 (q, J = 7.2 , 1H), 4.33 – 4.20 (m, 2H), 3.81 – 3.78 (m, 4H), 3.57 – 3.48 (m, 4H), 1.57 (d, J = 6.8, 3H), 1.33 (t, J = 7.2, 3H).

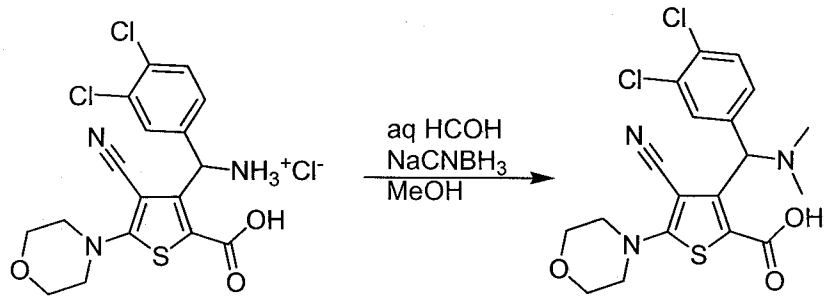
[00861] **Step 3:** 4-[1-(4-Chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (Compound **121**). To a solution of ethyl 4-[1-(4-chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (1.42 g, 0.00373 mol) in tetrahydrofuran (30.2 mL, 0.373 mol) and methanol (6.04 mL, 0.149 mol) was added sodium hydroxide (1.0N in water, 29.8 mL, 0.0298 mol), and the resulting cloudy mixture was heated at 65 °C for 5 hours. The reaction was cooled to room temperature, diluted with water, and adjusted to pH 3.0 via addition of 1N aqueous HCl. The mixture was transferred to a separatory funnel and the layers separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 4-[1-(4-chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (**121**) (1.21 g, yield 92%) as a white solid. LCMS: (FA) ES+ 353; ^{1}H NMR (400 MHz, DMSO) δ 12.70 (bs, 1H), 7.37 – 7.34 (m, 2H), 7.33 – 7.30 (m, 2H), 5.09 (q, J = 7.2, 1H), 3.69 – 3.76 (m, 4H), 3.48 – 3.39 (m, 4H), 1.49 (d, J = 6.8, 3H).

[00862] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 48.

304	LC/MS: (AA) ES+ 381, 383
332	LC/MS: (AA) ES+ 387, 389

[00863]

[00864] Example 49: Synthesis of 4-cyano-3-[(3,4-dichlorophenyl)(dimethylamino)methyl]-5-(morpholin-4-yl)thiophene- 2-carboxylic acid (Compound 362)



[00865] Step 1: 4-cyano-3-[(3,4-dichlorophenyl)(dimethylamino)methyl]-5-(morpholin-4-yl)thiophene- 2-carboxylic acid.

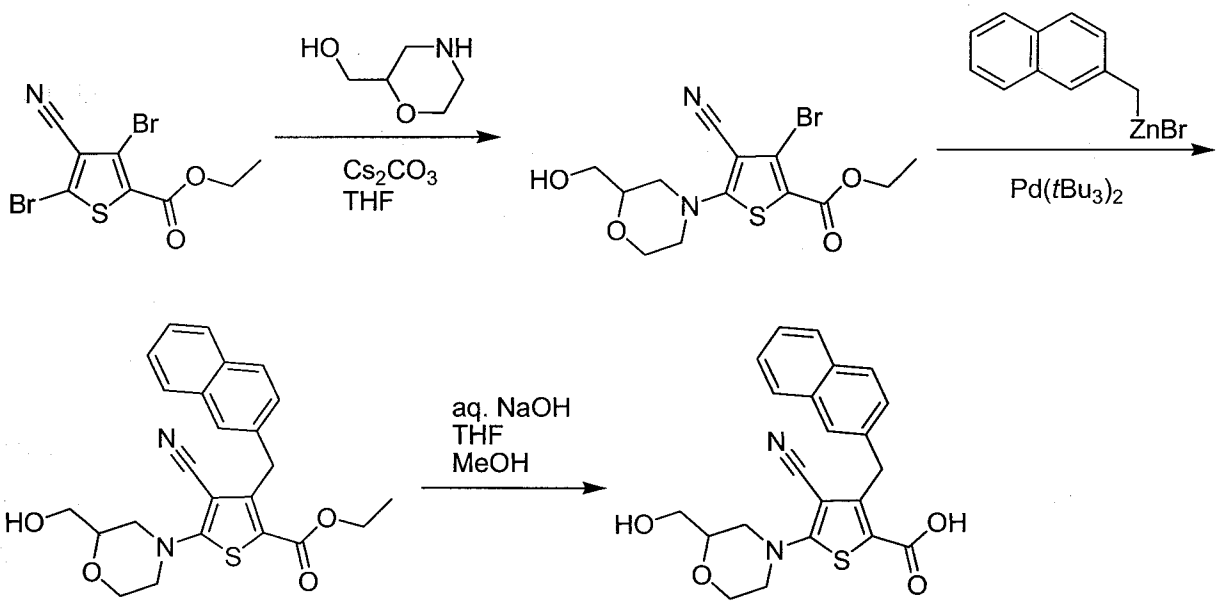
[00866] To a suspension of 3-[amino(3,4-dichlorophenyl)methyl]-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylic acid•HCl (186.0 mg, 0.4145 mmol, prepared according to Example 6) in methanol (8.09 mL, 0.101 mol) was added 10 M of formaldehyde in water (74.00 uL, 0.9119 mmol), and sodium cyanoborohydride (130 mg, 2.07 mmol) . Stirred at rt under argon for 16 hours. Added 10 M of formaldehyde in water soln (74.00 uL, 0.919 mmol) and sodium cyanoborohydride (0.130 g, 2.07 mmol) and stirred at rt for 72 hours. Quenched reaction with saturated aqueous sodium bicarbonate solution, added EtOAc, separated layers, extracted again w/EtOAc, combined organics, washed organics with saturated sodium bicarbonate, brine, dried over Na_2SO_4, filtered, added Celite to filtrate, and concentrated *in vacuo*. Purification of dry load via silica gel column chromatography (gradient elution: 100% DCM to 8% MeOH in DCM) afforded racemic 4-cyano-3-[(3,4-dichlorophenyl)(dimethylamino)methyl]-5-(morpholin-4-yl)thiophene- 2-carboxylic acid (134 mg, 68%) as an off-white solid. LC/MS: (FA) 440, 442, 444; ^{1}H NMR (400 MHz, DMSO) δ 7.80-7.76 (m, 2 H), 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 5.26 (s, 1H), 3.74 – 3.64 (m, 4H), 3.53 – 3.38 (m, 4H), 2.76 (s, 3H), 2.42 (s, 3H). Combined with another batch of 134 mg racemate for chiral HPLC to obtain pure enantiomers. Purified on IC 4.6X250 mm with 90/10/0.1 HEX/ETOH/DEA 10 uL Injection at 1.0 mL/min for 70 min. CD AT 254 nm to obtain separated enantiomers as the diethylamine salts. Each compound Peak1 and Peak2 were separately dissolved in water, acidified to pH of 2 with aqueous 1N HCl solution, extracted w/EtOAc, 3x, combined organics and washed w/brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*, added water, freeze-dried, lyophilized overnight to recover parent compound. Peak 1 (103 mg, tan solid, overall 27% yield) LC/MS: (FA) 440, 442, 444; ^{1}H NMR (400 MHz, DMSO) δ 7.80-7.76 (m, 2 H), 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 5.26 (s, 1H), 3.74 – 3.64 (m, 4H), 3.53 – 3.38 (m, 4H), 2.76 (s, 3H), 2.42 (s, 3H). Peak 2 (80 mg, beige solid, overall 20% yield) LC/MS: (FA) 440, 442, 444; ^{1}H NMR (400 MHz, DMSO) δ 7.80-7.76 (m, 2

H),, 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 5.26 (s, 1H), 3.74 – 3.64 (m, 4H), 3.53 – 3.38 (m, 4H), 2.76 (s, 3H), 2.42 (s, 3H).

[00867] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 49.

336	LC/MS: (FA) ES+ 440, 442, 444
351	LC/MS: (FA) ES+ 406, 408

[00868] Example 50: Synthesis of 4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]-3-(2-naphthylmethyl)thiophene-2-carboxylic acid (Compound 297).



[00869] Step 1: ethyl 3-bromo-4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]thiophene-2-carboxylate

[00870] Ethyl 3,5-dibromo-4-cyanothiophene-2-carboxylate (0.360 g, 1.06 mmol), cesium carbonate (1.05 g, 3.21 mmol), 2-hydroxymethylmorpholine (137 mg, 1.17 mmol), and tetrahydrofuran (4.5 mL, 36 mmol) were combined in a 15 mL pressure vessel equipped with a stir bar. The vessel was sealed, and the rxn was heated @ 90° C with stirring for 4 hours. The reaction was cooled to rt. The rxn was poured into water/saline. The reaction vessel was washed out with additional water, then ethyl acetate, and these were added to the quench which was then transferred to a separatory funnel. The aqueous layer was extracted 3X with EtOAc. The extracts were combined, washed with saline, dried over Na_2SO_4, filtered, added Celite, concentrated *in vacuo*, and dried on high vac 30 min. Purified dry load via silica gel chromatography (gradient elution: 0-60% EtOAc/hexanes) to give 163 mg solid (41% yield). ^{1}H NMR

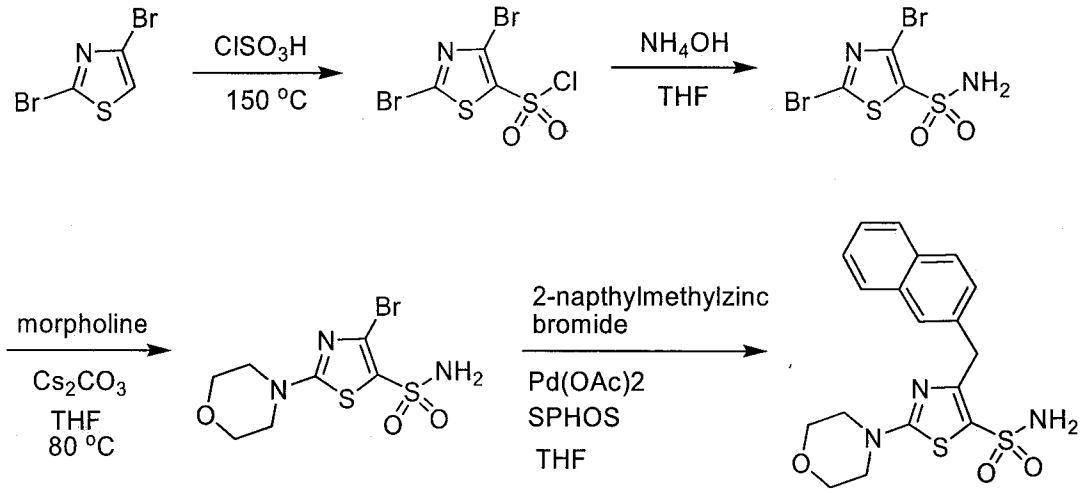
(400 MHz, DMSO) δ 4.91 (t, *J* = 5.7 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.99-3.92 (m, 3 H), 3.69-3.58 (m, 2 H), 3.50 (dt, *J* = 10.5, 5.2 Hz, 1H), 3.41 (dt, *J* = 11.5, 5.8 Hz, 1H), 3.37 – 3.27 (m, 1H, under H2O peak),3.15 – 3.08 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

[00871] Step 2: ethyl 4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]-3-(2-naphthylmethyl)thiophene- 2-carboxylate and 4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]-3-(2-naphthylmethyl)thiophene- 2-carboxylic acid

[00872] Bis(tri-t-butylphosphine)palladium(0) (16.44 mg, 0.03218 mmol) and ethyl 3-bromo-4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]thiophene-2-carboxylate (161.0 mg, 0.4290 mmol) were combined in a dry round bottom flask equipped with a stirbar and septum. Evacuated/refilled with argon 3X, then added 0.50 M solution of 2-naphthylmethylzinc bromide in tetrahydrofuran(1.72 mL, 0.858 mmol) via a syringe to give a brown soln. The reaction was stirred at rt for 5 minutes, then at 60° C for 1.5 h. Bis(tri-t-butylphosphine)palladium(0) (38.4 mg, 0.0751 mmol) and 0.50 M solution of 2-naphthylmethylzinc bromide in tetrahydrofuran (1.29 mL, 0.644 mmol) was added, degassed 2x and flushed w/argon, heated at 60 °C 1h. The reaction was cooled to rt, diluted with EtOAc, and then quenched with sat. NH4Cl solution. Transferred quenched mixture to a separatory funnel, separated layers, and extracted the aqueous layer once more with EtOAc, combined organics, washed w/brine, dried over Na2SO4, filtered, and concentrated *in vacuo*. Added EtOAc and Celite, rotovapped, dried on high vac 30 min. Purified dry load onto 40 g ISCO column (gradient elution: 0-55% EtOAc/hexanes) to obtain 119 mg yellow oil (64% yield). LC/MS (AA) ES+437.

[00873] To ethyl-4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]-3-(2-naphthylmethyl)thiophene-2-carboxylate (0.116 g, 0.266 mmol) in a rbf equipped with a stirbar was added tetrahydrofuran (2.96 mL, 36.4 mmol) and 1.000 M of sodium hydroxide in water (2.22 mL, 2.22 mmol) and methanol (1.48 mL, 36.5 mmol). The resulting yellow mixture was stirred at rt for 16 h. The reaction was quenched with the addition of 2.5 mL of 1N HCl in water to pH of 2, and added EtOAc Transferred to separatory funnel, separated layers, extracted aquoeous 2x w/EtOAc, combined organics, washed w/brine, dried over Na2SO4, filtered, added Celite, and concentrate *in vacuo*. Purified dry load *via* silica gel chromatography on 40 g ISCO column (gradient elution 0-20% MeOH/DCM) to give 66 mg white solid (61% yield). LC/MS (FA) ES+409; ES-407; ^{1}H NMR (400 MHz, DMSO) δ 13.45 (br s, 1H), 7.88-7.77 (m, 3 H), 4.7 Hz, 3H), 7.69 (s, 1H), 7.51 – 7.42 (m, 3H), 4.87 (s, 1H), 4.57 – 4.47 (m, 2H), 3.94-3.77 (m, 3 H), 3.65-3.53 (m, 2 H), 3.60 – 3.52 (m, 1H), 3.47 (dd, *J* = 11.3, 5.0 Hz, 1H), 3.37 (dd, *J* = 11.3, 5.8 Hz, 1H, overlaps with H_2O peak), 3.15 (td, *J* = 12.1, 3.4 Hz, 1H), 2.99 – 2.89 (m, 1H).

[00874] Example 10: Synthesis of 2-morpholino-4-(naphthalen-2-ylmethyl)thiazole-5-sulfonamide (Compound 329)



[00875] **Step 1, Preparation of 2,4-dibromothiazole-5-sulfonyl chloride**

[00876] To a flask containing chlorosulfonic acid (51.0 mL, 767 mmol) was added 2,4-dibromothiazole (10.2 g, 42.0 mmol) with stirring over 15 minutes. The resulting solution was heated to 150 degrees overnight. The reaction was quenched by carefully and slowly pouring onto ice (500 mL). The resulting precipitate was extracted with ethyl acetate (2 x 200 mL) and the combined organic layers were washed with water, dried, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 0/100→15/85) to give 8.1 g (56 % yield) of the title compound as a yellow oil which partially solidified. ^{13}C NMR (400 MHz, $CDCl_3$) δ: 145.04, 138.78, 131.81.

[00877] **Step 2, Preparation of 2,4-dibromothiazole-5-sulfonamide**

[00878] To a mixture of 2,4-dibromothiazole-5-sulfonyl chloride (3.17 g, 9.28 mmol) in THF (51.4 mL) was added 33% aqueous NH_4OH (24.1 mL, 278 mmol) and the reaction was stirred at room temperature for 30 minutes. The reaction was concentrated in vacuo and the residue was taken up in ethyl acetate (100 mL) and water (100 mL). The aqueous layer was extracted with ethyl acetate (50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL), then dried and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→20/80) to give 1.7 g (57 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 321, 323, 325. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.33 (s, 2H).

[00879] **Step 3, Preparation of 4-bromo-2-morpholinothiazole-5-sulfonamide**

[00880] A mixture of 2,4-dibromothiazole-5-sulfonamide (0.515 g, 1.60 mmol), morpholine (0.153 mL, 1.76 mmol), THF (4.22 mL) and cesium carbonate (1.56 g, 4.80 mmol) in a sealed tube was heated to 80 degrees for 4 hours. The cooled reaction was concentrated in vacuo and the residue was taken up in ethyl acetate (50 mL) and water (25 mL). The layers were separated and the organic layer was washed with water (15 mL), dried and concentrated in vacuo. The residue was purified by silica gel

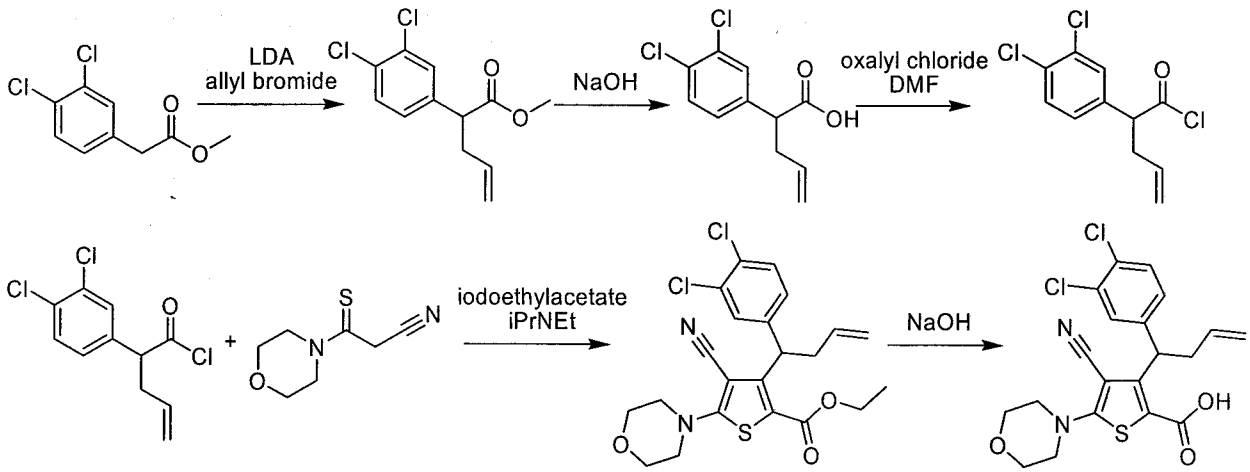
chromatography (ethyl acetate/DCM = 0/100→50/50) to give 230 mg (44 % yield) of the title compound as a white solid. LC/MS (FA) ES+ 328, 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.76 (s, 2H), 3.69-3.66 (m, 4H), 3.43-3.40 (m, 4H).

[00881] Step 4, Preparation of 2-morpholino-4-(naphthalen-2-ylmethyl)thiazole-5-sulfonamide

[00882] To a dried flask was added 4-bromo-2-morpholinothiazole-5-sulfonamide (194 mg, 0.591 mmol), THF (4.79 mL), palladium(II) acetate (1.33 mg, 0.00591 mmol) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (4.85 mg, 0.0118 mmol). The mixture was stirred for 5 minutes, and a 0.500 M solution of 2-napthylmethylzinc bromide in THF (4.14 mL, 2.04 mmol) was then added dropwise over 30 minutes. The reaction was stirred at room temperature for 1 hour and quenched with saturated ammonium chloride (10 mL). The reaction was extracted with ethyl acetate (2 x 25 mL) and the combined organic layers were washed with water (15 mL), dried and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→40/60) which gave a mixture of the desired product with residual 4-bromo-2-morpholinothiazole-5-sulfonamide. This material was purified by preparative reverse phase chromatography to give 51 mg (22 % yield) of the title compound as a white solid. LC/MS (FA) ES+ 390. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.85-7.77 (m, 4H), 7.71 (bs, 2H), 7.50-7.42 (m, 3H), 4.25 (s, 2H), 3.64-3.61 (m, 4H), 3.35-3.32 (m, 4H).

[00883]

[00884] Example 51: Synthesis of 4-cyano-3-[1-(3,4-dichlorophenyl)but-3-en-1-yl]-5-(morpholin-4-yl)thiophene-2-carboxylate (Compound 355)



[00885] Step 1: To a solution of N,N-diisopropylamine (1.79 mL, 12.8 mmol) in tetrahydrofuran (10.0 mL, 123 mmol) was added 2.50 M of n-butyllithium in hexane(4.68 mL, 11.7 mmol) dropwise at 0 °C. The solution was stirred under an atmosphere of Nitrogen for 10 min, and then cooled to -78 °C. A solution of methyl 3,4-dichlorophenylacetate (2.27 g, 10.4

mmol) in tetrahydrofuran (10.0 mL) was added to the LDA solution dropwise via cannula. After 10min of stirring, the reaction was warmed to 0 °C for 1 hr. The solution was cooled back to -78 °C, and allyl bromide (2.24 mL, 25.9 mmol) was added in one portion. In 10 min, the reaction was warmed back to 0 °C. After 1 hr of stirring, the reaction was quenched with NH_4Cl sat soln and extracted with EtOAc(x3). The combined organic layer was dried and concentrated to provide an orange oil. Further purification on a silica gel column (gradient elution, 0-10% EtOAc/hexanes) provided methyl 2-(3,4-dichlorophenyl)pent-4-enoate as a colorless oil (2.47 g, 92.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.18 – 7.12 (dd, J = 8.3, 2.1 Hz, 1H), 5.73 – 5.60 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.12 – 4.98 (m, 2H), 3.70 – 3.64 (s, 3H), 3.63 – 3.55 (t, J = 7.8 Hz, 1H), 2.85 – 2.71 (m, 1H), 2.55 – 2.43 (m, 1H).

[00886] **Step2**: To a solution of methyl 2-(3,4-dichlorophenyl)pent-4-enoate (2.47 g, 9.53 mmol) in tetrahydrofuran (15.0 mL) was added a solution of lithium hydroxide monohydrate (2.00 g, 47.6 mmol) in water (15.0 mL). The mixture was vigorously stirred at rt for 12 hrs. The resulting mixture was acidified by addition of 12.0 M of hydrochloric acid in water (3.97 mL, 47.6 mmol) at 0 °C, and extracted with EtOAc(x3). The combined organic layer was dried and concentrated to provide 2-(3,4-dichlorophenyl)pent-4-enoic acid as a yellow syrup (2.65 g, quantative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.21 – 7.11 (dd, J = 8.3, 2.1 Hz, 1H), 5.76 – 5.59 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 5.14 – 4.99 (m, 2H), 3.65 – 3.56 (t, J = 7.7 Hz, 1H), 2.88 – 2.74 (dt, J = 14.8, 7.5 Hz, 1H), 2.58 – 2.43 (dt, J = 14.3, 6.9 Hz, 1H).

[00887] **Step3**: To a soln of 2-(3,4-dichlorophenyl)pent-4-enoic acid (2.34 g, 9.53 mmol) in methylene chloride (25.0 mL) was added oxalyl chloride (1.61 mL, 19.0 mmol) followed by N,N-dimethylformamide (73.8 uL, 0.953 mmol) After 1 hr of stirring at rt, the solution was concentrated to provide 2-(3,4-dichlorophenyl)pent-4-enoyl chloride as a yellow oil (2.70 g, quantative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (d, J = 8.3 Hz, 1H), 7.40 – 7.36 (d, J = 2.2 Hz, 1H), 7.17 – 7.10 (dd, J = 8.3, 2.2 Hz, 1H), 5.73 – 5.57 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.15 – 5.06 (m, 2H), 4.06 – 3.97 (t, J = 7.6 Hz, 1H), 2.97 – 2.83 (m, 1H), 2.61 – 2.49 (m, 1H).

[00888] **Step4**: To a solution of 2-(3,4-dichlorophenyl)pent-4-enoyl chloride (2.51 g, 9.53 mmol) and 3-morpholin-4-yl-3-thioxopropanenitrile (1.62 g, 9.53 mmol) in acetonitrile (40.0 mL) in a 100 mL round bottom flask was added N,N-diisopropylethylamine (1.82 mL, 10.5 mmol), and the resulting deep orange/red solution was stirred at room temp for 1 hr. To the resulting mixture was added N,N-diisopropylethylamine (4.15 mL, 23.8 mmol) and then ethyl

iodoacetate (1.24 mL, 10.5 mmol). The flask was fitted with a reflux condenser and the reaction was heated to reflux over 48 hrs. The mixture was concentrated and distributed between $NaHCO_3$(aq) saturated solution and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined org layer was washed with brine, dried, and concentrated to provide a dark syrup. Purification on a silica gel column (gradient elution 3-30% EtOAc/hexanes) provided ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)but-3-en-1-yl]-5-(morpholin-4-yl)thiophene- 2-carboxylate (704 mg, 15.9% yield). LCMS: (AA) ES+ 465, 467, 469; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 1H), 7.41 – 7.33 (m, 1H), 7.31 – 7.27 (m, 1H), 5.82 – 5.66 (ddt, J = 17.2, 10.1, 6.8 Hz, 1H), 5.62 – 5.50 (t, J = 8.2 Hz, 1H), 5.16 – 5.08 (dd, J = 17.1, 1.6 Hz, 1H), 5.04 – 4.94 (dd, J = 10.2, 1.5 Hz, 1H), 4.35 – 4.27 (q, J = 7.1 Hz, 2H), 3.86 – 3.78 (m, 4H), 3.59 – 3.48 (m, 4H), 3.10 – 2.99 (h, J = 6.9 Hz, 2H), 1.40 – 1.31 (m, 3H).

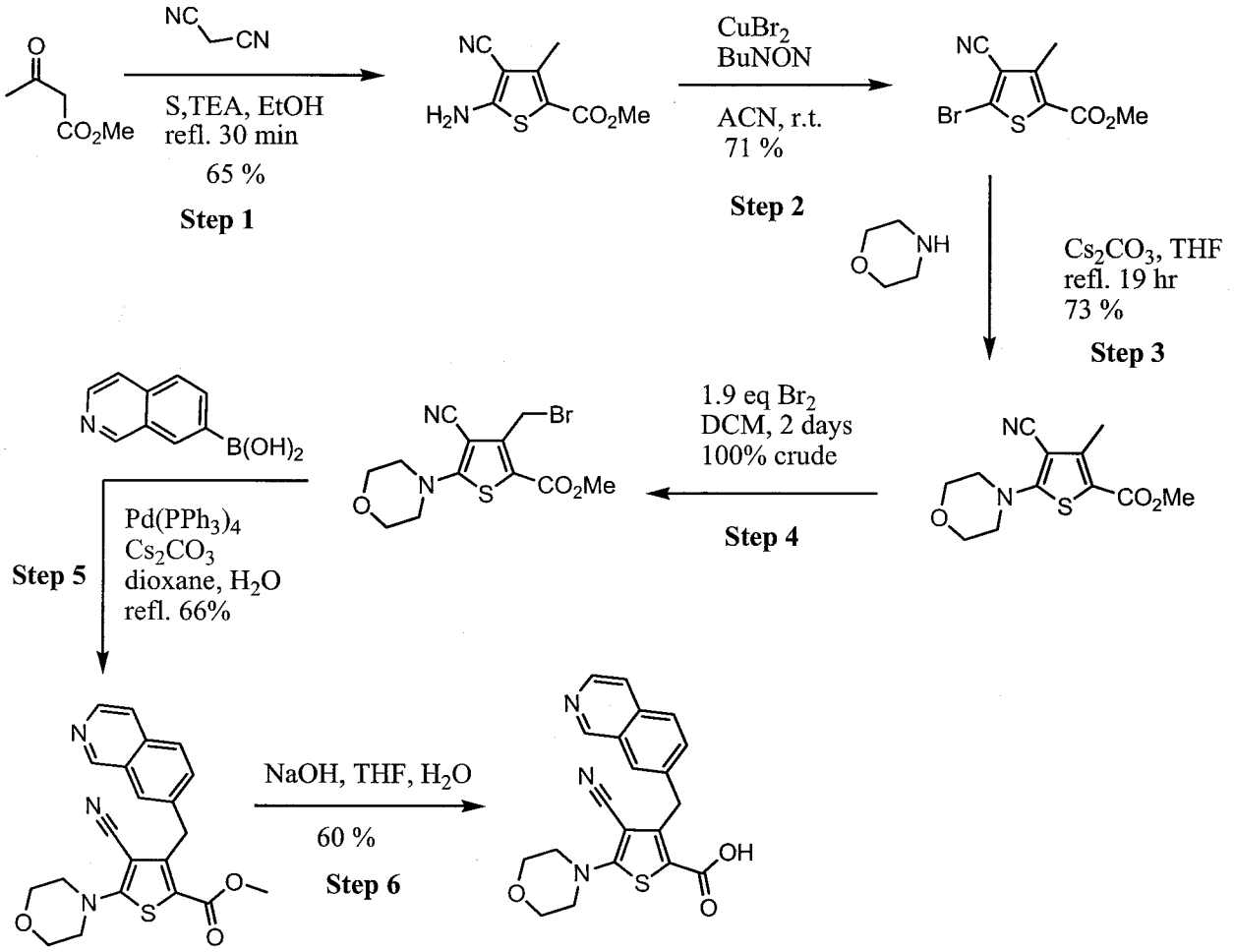
[00889] **Step5**: To a solution of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)but-3-en-1-yl]-5-(morpholin-4-yl)thiophene-2-carboxylate (0.211 g, 0.453 mmol) in tetrahydrofuran (8.00 mL) was added 1.000 M of sodium hydroxide in water(10.0 mL) and methanol (4.00 mL). The resulting mixture was stirred at room temp over 3 hrs. The volatiles were removed under reduced pressure, and the resulting mixture was acidified with conc. HCl soln to pH~2, and extracted with EtOAc(x3). The combined org layer was dried and concentrated to provide a purple syrup. Purification of the crude mixture on HPLC (AA, reverse phase) provided 4-cyano-3-[1-(3,4-dichlorophenyl)but-3-en-1-yl]-5-(morpholin-4-yl)thiophene- 2-carboxylic acid as a white solid (63 mg, 31.8% yield). LCMS: (AA) ES- 391, 393, 395; ^{1}H NMR (400 MHz, MeOD) δ 7.54 – 7.46 (d, J = 1.6 Hz, 1H), 7.45 – 7.35 (d, J = 8.4 Hz, 1H), 7.34 – 7.24 (dd, J = 8.4, 1.6 Hz, 1H), 5.88 – 5.68 (m, 2H), 5.16 – 5.05 (dd, J = 17.1, 1.7 Hz, 1H), 5.00 – 4.92 (m, 1H), 3.82 – 3.71 (t, J = 4.8 Hz, 4H), 3.51 – 3.40 (t, J = 4.8 Hz, 4H), 3.05 – 2.95 (m, 2H).

[00890] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 51.

307	LC/MS: (FA) ES- 412
308	LC/MS: (FA) ES- 413
321	LC/MS: (AA) ES+ 411, 413
326	LC/MS: (AA) ES+ 411
345	LC/MS: (FA) ES- 395
349	LC/MS: (FA) ES- 437

358	LC/MS: (FA) ES+ 399, 401
364	LC/MS: (FA) ES- 395
369	LC/MS: (AA) ES+ 411

[00891] Example 52: **Synthesis of 4-cyano-3-(isoquinolin-7-ylmethyl)-5-(morpholin-4-yl)thiophene-2-carboxylic acid (Compound 309)**



[00892] **Step 1: 5-Amino-4-cyano-3-methyl-thiophene-2-carboxylic acid ethyl ester:**

[00893] To a solution of 3-oxobutanoic acid, methyl ester (8.25 mL, 76.4 mmol), malononitrile (5.05 g, 76.4 mmol) and sulfur (2.45 g, 76.4 mmol) in anhydrous ethanol (100 mL, 2000 mmol) was added triethylamine (10.7 mL, 76.8 mmol). The mixture was heated to reflux for 30 min. The mixture was cooled to room temperature. The resulted crystal was collected by filtration and washed with MeOH, dried in vacuum to afford the product (9.25 g, yield 61.7%). LC/MS: (FA) ES- 195. ^{1}H NMR (400MHz, *d*-chloroform) δ 5.13 (s, br, 2H), 3.82 (s, 3H), 2.52 (s, 3H).

[00894] **Step 2 Methyl 5-bromo-4-cyano-3-methylthiophene-2-carboxylate:**

[00895] To a dark solution of Methyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate (6.65 g, 33.9 mmol) and copper(II) bromide (15.1 g, 67.8 mmol) in anhydrous acetonitrile (260 mL) was added slowly butyl nitrite (7.26 mL, 61.0 mmol) over 8 min. The mixture was stirred at room temperature for 70 min. The mixture was concentrated in rotavapor to give a black residue. The residue was dissolved in DCM, filtered through Celite. The filtrate was rotavaped with Celite. The Celite coated residue was dry loaded into a silica gel column and chromatographed using EtOAc/hexane (0/100 to 10/90) to give a white solid product (6.29 g, yield 71.4%). ^{1}H NMR (400MHz, *d*-chloroform) δ 3.89 (s, 3H), 2.67 (s, 3H)

[00896] **Step 3: Methyl 4-cyano-3-methyl-5-(morpholin-4-yl)thiophene-2-carboxylate:**

[00897] A mixture of methyl 5-bromo-4-cyano-3-methylthiophene-2-carboxylate (6.29 g, 24.2 mmol), morpholine (2.53 g, 29.0 mmol) and cesium carbonate (15.8 g, 48.4 mmol) in anhydrous Tetrahydrofuran (110 mL) was heated to reflux for 19 hours, and then cooled to room temperature. The mixture was filtered and washed with DCM. The filtrate was rotavaped with Celite. The coated Celite was dry loaded in a silica gel cartridge and chromatographed using MeOH/DCM (1/99) to give a white solid product (4.70 g, yield 73 %). LC/MS: (FA) ES$^+$ 267. ^{1}H NMR (400MHz, *d*-chloroform) δ 3.85 (m, 4H), 3.82 (s, 3H), 3.58 (m, 4H), 2.56 (s, 3H).

[00898] **Step 4: Methyl 3-(bromomethyl)-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylate:**

[00899] To the solution of methyl 4-cyano-3-methyl-5-(morpholin-4-yl)thiophene-2-carboxylate (0.500 g, 1.88 mmol) in anhydrous methylene chloride (15 mL, 230 mmol) was added a solution of bromine (0.409 g, 2.56 mmol) in anhydrous methylene chloride (5.0 mL, 78 mmol). The mixture was stirred at room temperature for 4 days. The mixture was evaporated under reduced pressure and dried in vacuum to give a crude product that was used without further purification (0.658g, contained 3.4% starting material, yield 96.6%). LC/MS: (FA) ES$^+$ 345, 347. ^{1}H NMR (400MHz, *d*-chloroform) δ 4.83 (s, 2H), 3.87 (s, 3H), 3.85 (m, 4H), 3.62 (m, 4H).

[00900] **Step 5: Methyl 4-cyano-3-(isoquinolin-7-ylmethyl)-5-(morpholin-4-yl)thiophene-2-carboxylate**

[00901] A mixture of methyl 3-(bromomethyl)-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylate (0.128 g, 0.371 mmol), isoquinoline-7-boronic acid (101 mg, 0.584 mmol), tetrakis(triphenylphosphine)palladium(0) (21.4 mg, 0.0185 mmol) and cesium carbonate (0.242 g, 0.742 mmol) was suspended in 1,4-dioxane (8.0 mL, 100 mmol) and Water (0.60 mL, 33 mmol) under N_2 atmosphere in a 20 mL vial. The vial was capped and heated to 90°C for 1 hour. The mixture was cooled to room temperature and concentrated in vacuum. The residue was suspended in DCM and filtered over a celite pad. The filtrate was chromatographed in a silica gel column using MeOH/DCM (0/100 to 3/97) to afford a solid product (103 mg, 66.4 %). LC/MS: (FA) ES$^+$ 394. ^{1}H NMR (400MHz, *d*-chloroform) δ

9.20 (s, 1H), 8.47 (d, J = 5.77 Hz, 1H), 7.87 (s, 1H), 7.73 (d, J = 5.77 Hz, 1H), 7.60 (d, J = 5.77 Hz, 1H), 7.44-7.48 (m, 1H), 4.60 (s, 2H), 3.86 (s, 3H), 3.84 (m, 4H), 3.59 (m, 4H).

[00902] Step 6: 4-cyano-3-(isoquinolin-7-ylmethyl)-5-(morpholin-4-yl)thiophene-2-carboxylic acid

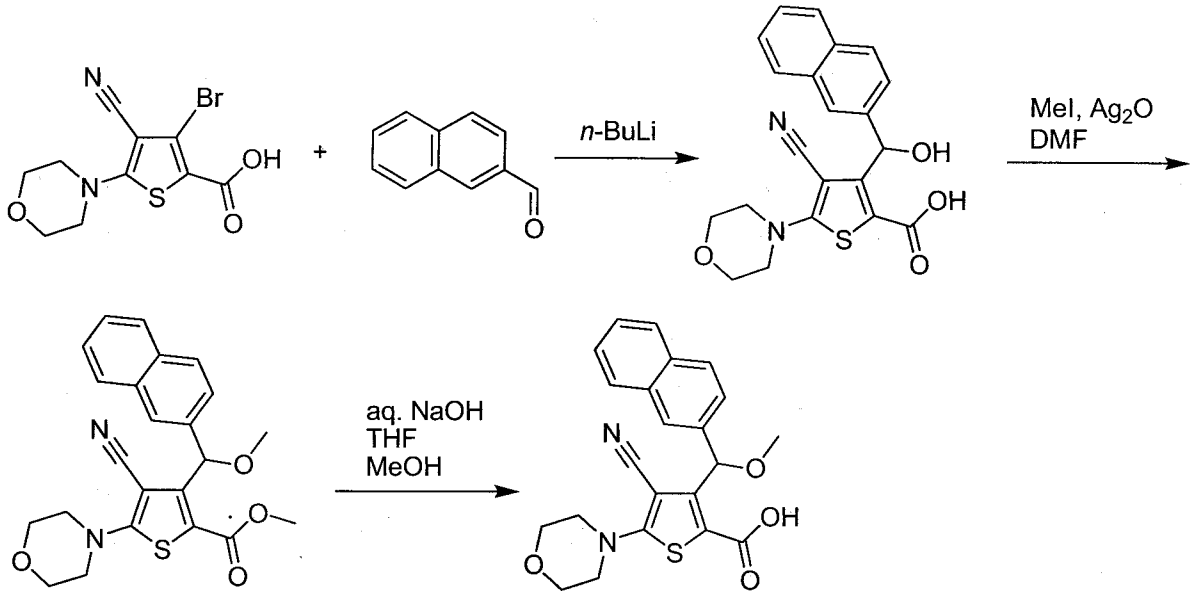
[00903] To the solution of methyl 4-cyano-3-(isoquinolin-7-ylmethyl)-5-(morpholin-4-yl)thiophene-2-carboxylate (0.103 g, 0.246 mmol) in tetrahydrofuran (15.0 mL, 185 mmol) was added 1.00 M of sodium hydroxide in water (3.80 mL, 3.80 mmol) , followed by water (4.0 mL, 220 mmol) and methanol (4.0 mL, 99 mmol). The homogeneous solution was stirred at room temperature for 18 hours. Acetic acid (270 mg, 4.5 mmol) was added and the mixture was concentrated in rotavapor. The residue was dissloved in DCM-MeOH and then concentrated with celite. The mixture was loaded in a cartridge and chromatographed in a silica gel column using AcOH/MeOH/DCM (0/0/100 to 0.5/4.5/95) to afford a white solid product (56.5 mg, yield 60.3%). LC/MS: (FA) ES^+ 380; ES^- 378. ^1H NMR (400MHz, *d*-chloroform) δ 9.23 (s, 1H), 8.45 (d, J = 5.77 Hz, 1H), 7.90 (d, J = 8.53 Hz, 1H), 7.84 (s, 1H), 7.76 (d, J = 5.77 Hz, 1H), 7.65 (dd, J = 8.53, 1.76 Hz, 1H), 4.53 (s, 2H), 3.72 (m, 4H), 3.52 (m, 4H).

[00904] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 52.

287	LC/MS: (AA) ES- 395
293	LC/MS: (AA) ES- 395
295	LC/MS: (AA) ES- 395
301	LC/MS: (AA) ES+ 409
305	LC/MS: (FA) ES- 381
311	LCMS: (FA) ES+ 385; ES- 383
312	LC/MS: (FA) ES+ 386, 388; ES- 384, 386
315	LC/MS: (FA) ES+ 397
324	LC/MS: (AA) ES- 395
330	LC/MS: (FA) ES+ 382; ES- 380
343	LC/MS: (AA) ES- 395
359	LC/MS: (FA) ES+ 402, 404 ; ES- 401, 403
361	LC/MS: (AA) ES+ 409

[00905] Example 53: Synthesis Example 3: Synthesis of 4-cyano-3-[methoxy(2-naphthyl)methyl]- 5-(morpholin-4- yl)thiophene-2- carboxylic acid (Compound

368).



[00906] Step 1: 4-cyano-3-[hydroxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid

A solution of 3-bromo-4-cyano-5-morpholinothiophene-2-carboxylic acid (5.50 g, 17.3 mmol) and 2-naphthalenecarboxaldehyde (8.12 g, 52.0 mmol) in tetrahydrofuran (550 mL) was cooled at -78 °C for 10 min, resulting in a white suspension. 2.5 M of n-butyllithium in hexane (27.7 mL, 69.4 mmol) was added dropwise, resulting in an orange solution. The solution was stirred at -78 °C for 10 min, then the cold bath was removed and the orange solution was stirred at ambient temperature for 40 minutes. The solution was quenched by the addition of methanol (21 mL) and acetic acid (3.9 mL), and the resulting mixture was let to warm up to rt O/N. The mixture was combined with a previous run on 2.86 g scale of the carboxylic acid, concentrated *in vacuo*, and azeotroped with toluene (2x50 mL). The crude solid was dissolved in MeOH, added Celite, rotavapped, dried on high vac O/N. The crude product was purified using dry load *via* silica gel chromatography on 330 g ISCO column (gradient elution 0-20% of (10%AcOH in MeOH) in DCM) to give 15.2 g solid containing 37wt% AcOH, for overall 92% yield. LC/MS (AA) ES-393; ^{1}H NMR (400 MHz, DMSO) δ 10.86 (d, J = 9.9 Hz, 1H), 7.86-7.81 (m, 4H), 7.70 (dd, J = 8.6, 1.6 Hz, 1H), 7.51 – 7.42 (m, 2H), 5.69 (d, J = 9.4 Hz, 1H), 3.73 – 3.68 (m, 4H), 3.39 – 3.33 (m, 4H).

[00907] Step 2: methyl 4-cyano-3-[methoxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylate

[00908] To a round bottom flask was added silver(I) oxide (56.15 g, 0.2423 mol), 4-cyano-3-[hydroxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid (15.17 g, 0.02423 mol), and N,N-dimethylformamide (66.2 mL), followed by methyl iodide (53.7 mL, 0.863 mol). Added another 10

mL DMF, sonicated to suspend/mix all solid. The reaction mixture was stirred at room temperature for 26 hours, then was diluted with EtOAc, filtered through a pad of Celite, concentrated filtrate *in vacuo*, azeotroped w/toluene (10x 10 mL), DCM (20 mL), dried on high vacuum pump. The rude material was used directly in the next step. LC/MS (AA) ES+423, ES+Na+445; ^{1}H NMR (400 MHz, DMSO) δ 7.97 (s, 1H), 7.91-7.86 (m, 3H), 7.53 – 7.48 (m, 3H), 6.62 (s, 1H), 3.85 (s, 3H), 3.72 – 3.69 (m, 4H), 3.52-3.50 (m, 4 H), 3.43 (s, 3H).

[00909] Step 3: 4-cyano-3-[methoxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid

[00910] To methyl 4-cyano-3-[methoxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylate (10.56 g, 25 mmol) in a round bottom flask equipped with a stirbar was added tetrahydrofuran (278 mL) and 1.000 M of sodium hydroxide in water (208 mL, 208 mmol). Methanol (139 mL) was added to the mixture, and the resulting yellow mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by the addition of 1N HCl aqueous solution to adjust the pH to 2 and EtOAc was added. The mixture was transferred to a separatory funnel, separated layers, extracted aqueous 2x w/EtOAc, combined organics, washed w/brine, dried over Na_2SO_4, filtered, added celite, rotavapped, dried on high vacuum for 45 min. The crude material was purified using a dry load on 330 g silica gel ISCO column (gradient elution: 0-20% MeOH/DCM) to obtain the product as an impure beige solid (9.8g). Took 2 g, redissolved in DCM, added Celite, rotovapped, dried on high vac 45 min. Repurified this portion of product on 120 g ISCO silica gel column (gradient elution: 0-12% MeOH/DCM) to obtain 2.0 g beige foam product (racemate). LC/MS (FA) ES-407; ^{1}H NMR (400 MHz, DMSO) δ 13.57 (s, 1H), 7.96 (s, 1H), 7.89-7.86 (m, 3H), 7.53 – 7.46 (m, 3H), 6.68 (s, 1H), 3.73 – 3.67 (m, 4H), 3.50 – 3.45 (m, 4H), 3.43 (s, 3H). Enantiomeric separation of the enantiomers was performed by chiral HPLC on CHIRALPAK IC 4.6X250 mm with 85/5/10/0.1% HEX/IPA/ETOH/DEA 10 uL Injection at 1.0 mL/min for 50 min.

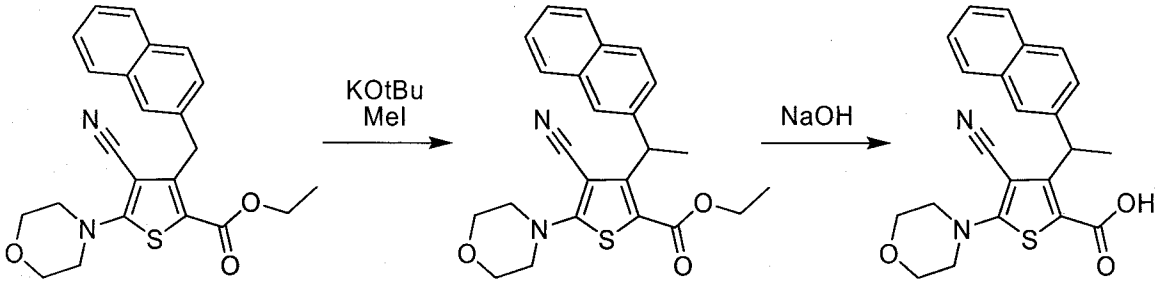
[00911] Step 4: 4-cyano-3-[methoxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid •Na

[00912] 4-cyano-3-[methoxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid (313.0 mg, 0.7663 mmol) was suspended in ethanol (7.159 mL, 122.6 mmol) and water (2.071 mL, 114.9 mmol) at room temperature. 1.030 M of sodium hydroxide in water (744.0 uL, 0.7663 mmol) was added slowly and the resulting solution was stirred for 10 min. The organic solvent was removed *in vacuo*. Added 40 ml water, freeze-dried, and lyophilized over night to give 322 mg amber solid (98% yield). LC/MS (FA) ES-407.5; ^{1}H NMR (400 MHz, DMSO) δ 7.99 (s, 1H), 7.88 – 7.76 (m, 3H), 7.61 (dd, J = 8.6, 1.3 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.24 (s, 1H), 3.68 – 3.65 (m, 4H), 3.37 (s, 3H), 3.26-3.33 (m, 4H).

[00913] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 53.

337	LC/MS: (FA) ES- 407

[00914] Example 54: Synthesis of Ethyl 4-cyano-5-(morpholin-4-yl)-3-[1-(2-naphthyl)ethyl]thiophene-2-carboxylate (Compound 367)



[00915] **Step 1**: A 1 L flask was charged with a big egg-shape stirring bar and ethyl 4-cyano-5-morpholin-4-yl-3-(2-naphthylmethyl)thiophene-2-carboxylate (14.5 g, 35.7 mmol). To the flask was added N,N-dimethylformamide (240 mL) and the mixture was evacuated and purged with nitrogen (x3). To the flask was added tetrahydrofuran (60 mL), and the mixture was stirred until it became a clear yellow solution. The solution was cooled to ~-25 °C in a dry ice-acetone bath (the temperature was actively controlled by slow addition of dry ice between -30~-40 °C). 1 M of Potassium tert-butoxide in tetrahydrofuran (42.8 mL) was added dropwise over 3 min. The mixture turned deep purple immediately. After the addition the mixture was stirred for 10 min at this temperature. Methyl iodide (11.1 mL, 178 mmol) was added over 1 min. By the end of addition the mixture turned light red. After stirring the resulting mixture at 0 °C for 10 min, the reaction was quenched by addition of 10 mL of water. All volatiles were removed under reduced pressure and the resulting mixture was distributed between brine and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layers were washed with 10% LiCl(aq) soln(x3), then brine, dried, and concentrated to provide a yellow syrup. Purification on a silica gel column (gradient elution 5-20% EtOAc/hexanes) provided Ethyl 4-cyano-5-(morpholin-4-yl)-3-[1-(2-naphthyl)ethyl]thiophene-2-carboxylate as a white solid (11.8g, 78.7% yield). LCMS: (AA) ES+ 421; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H), 7.82 – 7.70 (dd, J = 15.4, 8.1 Hz, 2H), 7.50 – 7.37 (m, 3H), 5.82 – 5.67 (q, J = 7.3 Hz, 1H), 4.40 – 4.25 (qd, J = 6.1, 5.0, 3.1 Hz, 2H), 3.86 – 3.72 (t, J = 4.8 Hz, 4H), 3.54 – 3.44 (t, J = 4.8 Hz, 4H), 1.95 – 1.85 (d, J = 7.3 Hz, 3H), 1.42 – 1.31 (t, J = 7.1 Hz, 3H).

[00916] **Step2**: Ethyl 4-cyano-5-(morpholin-4-yl)-3-[1-(2-naphthyl)ethyl]thiophene-2-carboxylate (13.3 g, 31.6 mmol) in tetrahydrofuran (200mL) and methanol (150mL) was stirred until the mixture turned into a clear solution. To the solution was added 1.000 M sodium hydroxide in water (158 mL). The resulting turbid mixture was vigorously stirred at rt for 12h. The volatiles were removed under reduced pressure, and the resulting aqueous solution was acidified by addition of 12.0 M of hydrochloric acid in water (15.9 mL, 191 mmol) at 0 °C, and then extracted with EtOAc(x3). The combined organic layers were washed with 1M HCl soln, dried, and concentrated to provide 4-cyano-5-(morpholin-4-yl)-3-[1-(2-naphthyl)ethyl]thiophene-2-carboxylic acid as a white solid (12.1g, 97.5% yield). 250 mg of the racemic mixture was purified on chiral prep HPLC to provide each enantiomer (115 mg each, >95% ee) (OJ column, elution with 85/5/10/0.1% hexane/iPrOH/EtOH/Et_2NH). LCMS: (AA) ES+ 393; ^{1}H NMR (400 MHz, MeOD) δ 7.85 – 7.76 (m, 3H), 7.76 – 7.71 (d, J = 8.6 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.38 – 7.29 (dd, J = 8.5, 1.7 Hz, 1H), 5.90 – 5.74 (q, J = 7.3 Hz, 1H), 3.82 – 3.69 (m, 4H), 3.52 – 3.43 (dd, J = 5.8, 4.0 Hz, 4H), 1.91 – 1.80 (d, J = 7.3 Hz, 3H).

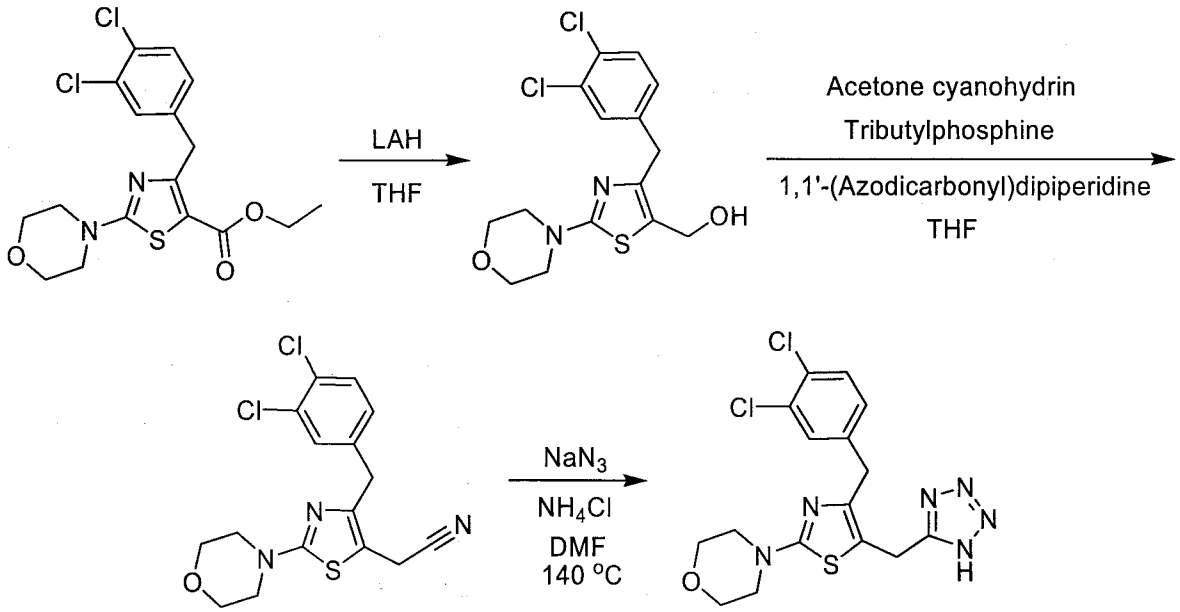
Step3: The active enantiomer 4-cyano-5-(morpholin-4-yl)-3-[1-(2-naphthyl)ethyl]thiophene-2-carboxylic acid (780 mg, 1.99 mmol) was suspended in ethanol (10.0 mL, 171 mmol). To the mixture was added 1.030 M of sodium hydroxide in water (2.00 mL, 2.06 mmol). The mixture was swirled and sonicated until it turned homogeneous. The solution was concentrated to provide 4-cyano-5-(morpholin- 4-yl)-3-[1-(2-naphthyl) ethyl]thiophene-2-carboxylic acid•Na as a yellow solid (785 mg, 95% yield). LCMS: (AA) ES+ 393; ^{1}H NMR (400 MHz, MeOD) δ 7.85 – 7.72 (m, 3H), 7.72 – 7.66 (d, J = 8.6 Hz, 1H), 7.45 – 7.30 (ddd, J = 12.6, 4.9, 2.2 Hz, 3H), 6.20 – 6.06 (q, J = 7.0 Hz, 1H), 3.81 – 3.70 (t, J = 4.8 Hz, 4H), 3.40 – 3.32 (t, J = 4.8 Hz, 4H), 1.88 – 1.78 (d, J = 7.4 Hz, 3H).

[00917] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 54.

306	LC/MS: (FA) ES+ 423
313	LC/MS: (FA) ES+ 423
322	LC/MS: (FA) ES+ 425
333	LC/MS: (AA) ES+ 393
346	LC/MS: (FA) ES+ 369
363	LC/MS: (FA) ES+ 423

365	LC/MS: (FA) ES+ 425
366	LC/MS: (AA) ES- 409, 411, 413

[00918] Example 55: Synthesis of 4-(5-((1H-tetrazol-5-yl)methyl)-4-(3,4-dichlorobenzyl)thiazol-2-yl)morpholine (Compound 350)



[00919] Step 1, Preparation of (4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)methanol

[00920] To a solution of ethyl 4-(3,4-dichlorobenzyl)-2-morpholinothiazole-5-carboxylate (4.92 g, 12.2 mmol) in THF (100 mL) was added a 2.00 M solution of LAH in THF (12.9 mL, 25.8 mmol) and the resulting solution was stirred for 2 hours at room temperature. The reaction was quenched by adding saturated NH_4Cl (26 mL) followed by 1M HCl (26 mL). Water (100 mL) and ethyl acetate (200 mL) were then added. The layers were separated and the organic layer was washed with brine (50 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→100/0) to give 2.87 g (65 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 359, 361. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.31 (m, 2H), 7.09 (dd, 1H, J = 6.0, 2.0 Hz), 4.66 (d, 2H, J = 1.2 Hz), 3.84 (s, 2H), 3.79-3.77 (m, 4H), 3.42-3.39 (m, 4H).

[00921] Step 2, Preparation of 2-(4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)acetonitrile

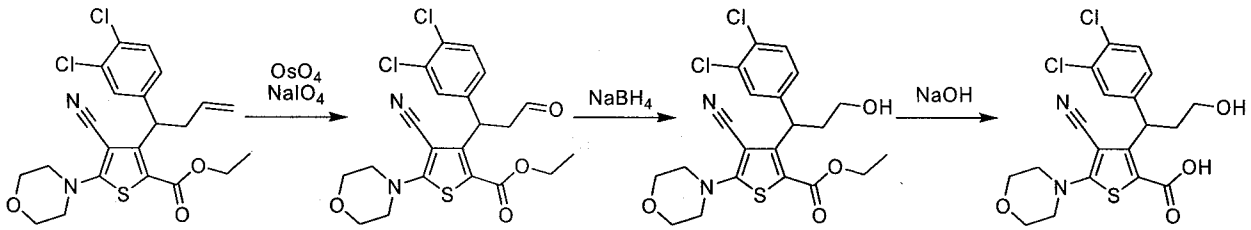
[00922] To a solution of (4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)methanol (1.19 g, 3.31 mmol) in THF (58.6 mL) was added acetone cyanohydrin (0.454 mL, 4.97 mmol), 1,1'-(azodicarbonyl)dipiperidine (1.67 g, 6.62 mmol) and tributylphosphine (1.65 mL, 6.62 mmol) and the reaction was stirred for 3 hours at room temperature. The reaction was concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→20/80) to give 551 mg (45 %

yield) of the title compound as a beige solid. LC/MS (FA) ES+ 368, 370. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, 1H, J = 6.0 Hz), 7.32 (d, 1H, J = 2.0 Hz), 7.07 (dd, 1H, J = 6.0, 2.0 Hz), 3.82 (s, 2H), 3.80-3.77 (m, 4H), 3.66 (s, 2H), 3.42-3.40 (m, 4H).

[00923] Step 3, Preparation of 4-(5-((1H-tetrazol-5-yl)methyl)-4-(3,4-dichlorobenzyl)thiazol-2-yl)morpholine

[00924] To a solution of 2-(4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)acetonitrile (87.0 mg, 0.236 mmol) in DMF (0.74 mL) was added sodium azide (21.6 mg, 0.332 mmol) and NH_4Cl (17.8 mg, 9.53 mmol) and the resulting mixture was heated to 140 degrees overnight. More sodium azide (43 mg, 0.66 mmol) and NH_4Cl (36 mg, 19 mmol) were added and the reaction was heated to 120 degrees overnight. The reaction was cooled and taken up in ethyl acetate (25 mL) and water (5 ml). The layers were separated and the organic layer was washed with water (3 x 5 mL).). The organic layer was dried and concentrated in vacuo. The residue was purified by preparative reverse phase chromatography to give 5 mg (5 % yield) of the title compound.as a white solid.LC/MS (FA) ES+ 411. 413. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.50 (d, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 2.0 Hz), 7.20 (dd, 1H, J = 8.0, 2.0 Hz), 4.41 (s, 2H), 3.88 (s, 2H), 3.65-3.62 (m, 4H), 3.32 (bs, 1H), 3.26-3.24 (m, 4H).

[00925] Example 56: Synthesis of 4-cyano-3-[1-(3,4-dichlorophenyl)-3-hydroxypropyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid (Compound 347)



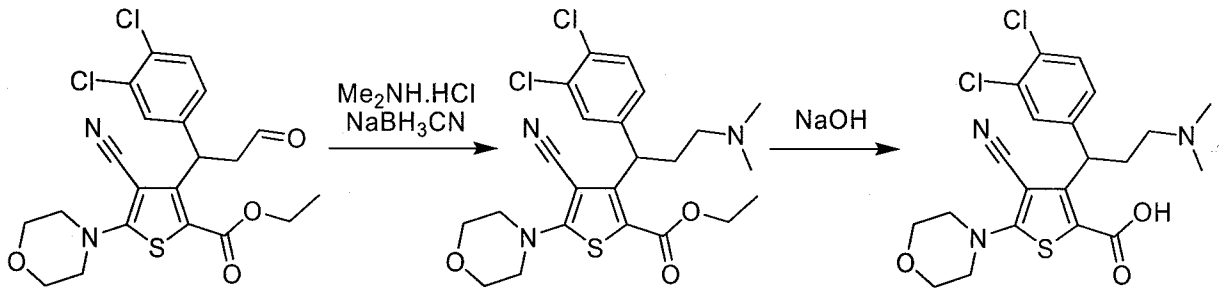
[00926] Step1: To a suspension of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)but-3-en-1-yl]-5-(morpholin-4-yl)thiophene-2-carboxylate (247 mg, 0.531 mmol) in 1,4-dioxane (6.00 mL) and water (2.00 mL) was added sodium metaperiodate (454 mg, 2.12 mmol), 2,6-lutidine (246 uL, 2.12 mmol), and 4% osmium tetroxide in water (4:96, osmium tetraoxide:water, 64.9 uL, 0.0106 mmol). The reaction was vigorously stirred at rt for 5 hrs. The mixture was filtered over a celite pad and the filtered solid was rinsed with EtOAc. The filtrate was washed with $NaHCO_3$(aq) saturated solution and the aqueous layer was extracted with EtOAc(x2). The combined organic layer was washed with 1N HCl soln and brine, dried, and concentrated. Purification on a silica gel column (gradient elution 5-50% EtOAc/hexanes) provided ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-oxopropyl]-5-(morpholin-4-yl)thiophene-2-carboxylate as a yellow syrup (108 mg, 43.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 – 9.73 (d, J = 1.3 Hz, 1H), 7.48 –

7.42 (d, J = 2.1 Hz, 1H), 7.42 – 7.32 (d, J = 8.4 Hz, 1H), 7.30 – 7.18 (m, 1H), 6.06 – 5.94 (t, J = 7.7 Hz, 1H), 4.38 – 4.26 (q, J = 7.1 Hz, 2H), 3.86 – 3.77 (t, J = 4.9 Hz, 4H), 3.62 – 3.51 (dd, J = 5.7, 4.0 Hz, 4H), 3.50 – 3.42 (m, 2H), 1.41 – 1.29 (m, 3H).

[00927] **Step2**: To a solution of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-oxopropyl]-5-(morpholin-4-yl)thiophene-2-carboxylate (50.0 mg, 0.107 mmol) in ethanol (1.00 mL) was added sodium tetrahydroborate (4.05 mg, 0.107 mmol). The mixture was stirred at rt for 1 hr. The reaction was quenched with 1.00 M of hydrochloric acid in water (0.428 mL) and distributed between $NaHCO_3$(aq) saturated solution and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was dried and concentrated to provide a white solid. Purification on a silica gel column (gradient elution 0-5% MeOH) provided ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-hydroxypropyl]-5-(morpholin-4-yl)thiophene-2-carboxylate as a colorless syrup (38 mg, 75.7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.35 (dd, *J* = 5.2, 3.1 Hz, 2H), 7.30 – 7.19 (m, 1H), 5.65 – 5.52 (t, *J* = 8.0 Hz, 1H), 4.42 – 4.26 (q, *J* = 7.1 Hz, 2H), 3.85 – 3.77 (t, *J* = 4.9 Hz, 4H), 3.76 – 3.65 (ddt, *J* = 13.0, 9.0, 4.6 Hz, 1H), 3.57 – 3.44 (t, *J* = 4.8 Hz, 5H), 2.69 – 2.58 (dd, *J* = 8.4, 4.1 Hz, 1H), 2.56 – 2.43 (dt, *J* = 8.1, 4.9 Hz, 2H), 1.44 – 1.32 (t, *J* = 7.1 Hz, 3H).

[00928] **Step3**: To a solution of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-hydroxypropyl]-5-(morpholin-4-yl)thiophene-2-carboxylate (38.0 mg, 0.0810 mmol) in tetrahydrofuran (1.00 mL) was added NaH 60% in mineral oil (60:40, Sodium hydride:mineral Oil, 3.56 mg, 0.0890 mmol). The mixture was heated to 60 °C for 3 hrs. The reaction was cooled to rt and distributed between brine and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was washed with brine, dried, and concentrated to provide a yellow solid. Purification on HPLC (reverse phase, AA) provided 4-cyano-3-[1-(3,4-dichlorophenyl)-3-hydroxypropyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid as a white solid (6.5mg, 18.2% yield). LCMS: (AA) ES+ 441, 443, 445; ^{1}H NMR (400 MHz, MeOD) δ 7.50 – 7.45 (s, 1H), 7.45 – 7.37 (d, *J* = 8.4 Hz, 1H), 7.30 – 7.22 (m, 1H), 5.79 – 5.63 (m, 1H), 3.83 – 3.71 (t, *J* = 4.8 Hz, 4H), 3.60 – 3.50 (q, *J* = 6.9, 6.0 Hz, 2H), 3.50 – 3.41 (d, *J* = 3.2 Hz, 4H), 2.52 – 2.37 (m, 2H).

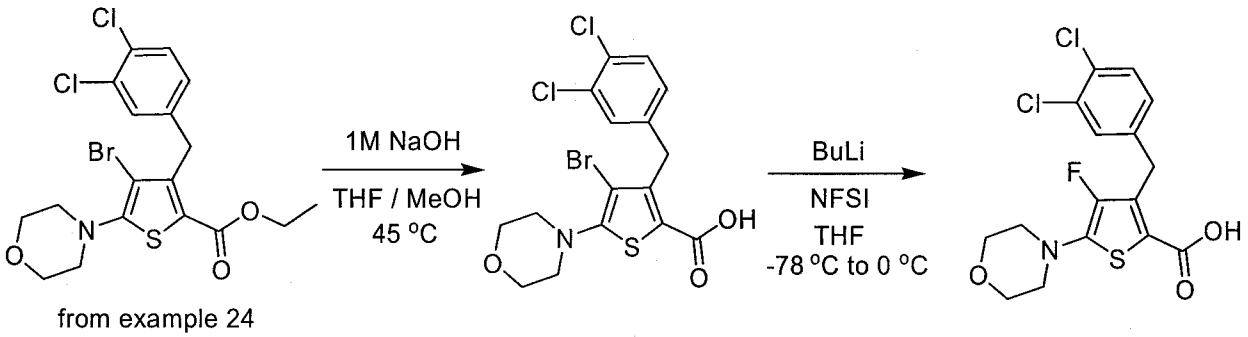
[00929] Example 57: Synthesis of 4-cyano-3-[1-(3,4-dichlorophenyl)-3-(dimethylamino)propyl]-5-(morpholin- 4-yl)thiophene-2-carboxylic acid (Compound 331)



[00930] **Step1**: To a solution of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-oxopropyl]-5-(morpholin-4-yl)thiophene-2-carboxylate (38.0 mg, 0.0813 mmol) (from example 56, step 1) in methanol (1.00 mL) was added dimethylamine hydrochloride (9.94 mg, 0.122 mmol), sodium acetate (8.00 mg, 0.0976 mmol), and sodium cyanoborohydride (6.13 mg, 0.0976 mmol). The reaction was stirred at rt for 2h. The mixture was distributed between $NaHCO_3$(aq) saturated solution and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was dried and concentrated. Purification on a silica gel column (gradient elution, 0-15% MeOH/CH_2Cl_2) provided ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-(dimethylamino)propyl]-5-(morpholin- 4-yl)thiophene-2-carboxylate as a yellow syrup (29.0 mg, 71.8% yield). LCMS: (AA) ES+ 496, 498, 500; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.44 (d, J = 1.9 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.33 – 7.27 (m, 1H), 5.54 – 5.40 (t, J = 7.7 Hz, 1H), 4.38 – 4.27 (q, J = 7.1 Hz, 2H), 3.88 – 3.76 (t, J = 4.9 Hz, 4H), 3.58 – 3.49 (dd, J = 5.7, 4.0 Hz, 4H), 2.57 – 2.31 (m, 3H), 2.29 – 2.24 (s, 6H), 2.24 – 2.16 (m, 1H), 1.41 – 1.30 (t, J = 7.1 Hz, 3H).

[00931] **Step2**: To a solution of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-(dimethylamino)propyl]-5-(morpholin-4-yl)thiophene-2-carboxylate (29.0 mg, 0.0584 mmol) in methanol (0.500 mL) was added 1.030 M of sodium hydroxide in water (284 uL, 0.284 mmol). The reaction was stirred at rt over 2 days. The mixture was neutralized with 1.00 M of hydrochloric acid in water(0.292 mL), diluted with 5 mL of water and extracted with 10% MeOH/$CHCl_3$ (x5). The combined organic layer was dried and concentrated, and the resulting white syrup/solid was lyophilized to provide 4-cyano-3-[1-(3,4-dichlorophenyl)-3-(dimethylamino)propyl]-5-(morpholin- 4-yl)thiophene-2-carboxylic acid as a white solid (26 mg, 95% yield). LCMS: (AA) ES+ 468, 470, 472; ^{1}H NMR (400 MHz, DMSO) δ 7.63 – 7.52 (d, J = 8.4 Hz, 1H), 7.44 – 7.37 (s, 1H), 7.15 – 7.02 (d, J = 8.1 Hz, 1H), 5.49 – 5.34 (d, J = 9.4 Hz, 1H), 3.73 – 3.63 (t, J = 4.8 Hz, 4H), 3.38 – 3.31 (dd, J = 6.2, 4.0 Hz, 4H), 3.13 – 2.97 (s, 1H), 2.85 – 2.73 (s, 1H), 2.72 – 2.60 (s, 6H), 2.56 – 2.52 (m, 1H).

[00932] Example 58: Synthesis of 3-(3,4-dichlorobenzyl)-4-fluoro-5-morpholinothiophene-2-carboxylic acid (Compound 320)



from example 24

[00933] Step 1, Preparation of 4-bromo-3-(3,4-dichlorobenzyl)-5-morpholinothiophene-2-carboxylic acid

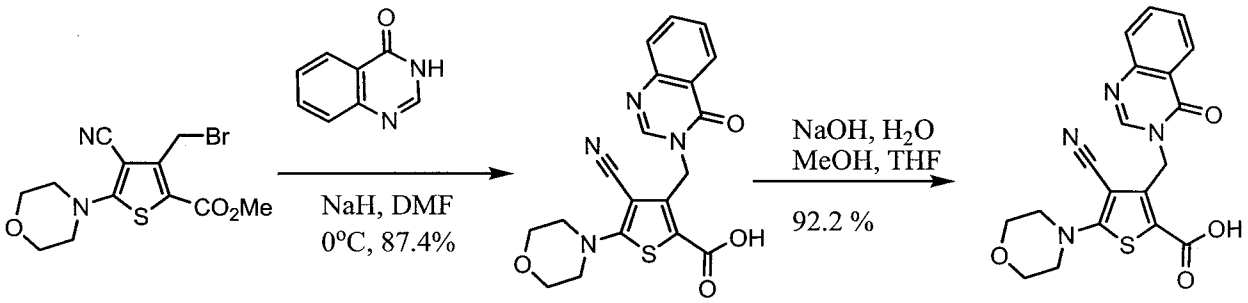
[00934] To a solution of ethyl 4-bromo-3-(3,4-dichlorobenzyl)-5-morpholinothiophene-2-carboxylate (109 mg, 0.227 mmol) in THF (1.8 mL) and MeOH (0.37 mL) was added 1.00 M aqueous NaOH (1.82 mL, 1.82 mmol) and the resulting mixture was stirred at 45 °C overnight. The reaction was diluted with water (5 mL) and acidified to pH = 3 with 1 N HCl. The mixture was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were dried, filtered and concentrated in vacuo to give 92 mg (90% yield) of a white solid which was used as is in the next step. LC/MS (AA) ES+ 450, 452, 454. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.21 (bs, 1H), 7.52 (d, 1H, J = 8.0 Hz), 7.39 (d, 1H, 2.0 Hz), 7.09 (dd, 1H, J = 8.0, 2.0 Hz), 4.36 (s, 2H), 3.74-3.71 (m, 4H), 3.13-3.11 (m, 4H).

[00935] Step 2, Preparation of 3-(3,4-dichlorobenzyl)-4-fluoro-5-morpholinothiophene-2-carboxylic acid

[00936] To a solution of 4-bromo-3-(3,4-dichlorobenzyl)-5-morpholinothiophene-2-carboxylic acid (89.0 mg, 0.197 mmol) in THF (3.00 mL) in a dry-ice/acetone bath was added 1.60 M BuLi in hexanes (0.271 mL, 0.434 mmol) and the resulting solution was stirred for 10 minutes at -78 °C. A solution of N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (93.3 mg, 0.296 mmol) in THF (0.70 mL) was then added and the reaction was allowed to warm to 0 °C. The reaction was quenched with saturated NH_4Cl (5 mL) and ethyl acetate (15 mL) was then added. The layers were separated and the aqueous layer was acidified to pH = 3 with 1N HCl. The acidic aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→15/85) to give 31 mg of product. This material was purified by preparative reverse phase chromatography to give 9 mg (10 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 390, 392. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.04 (bs, 1H), 7.54 (d, 1H, J = 8.0

Hz), 7.44 (d, 1H, J = 1.6 Hz), 7.16 (dd, 1H, J = 8.0, 1.6 Hz), 4.21 (s, 2H), 3.71-3.68 (m, 4H), 3.14-3.12 (m, 4H).

[00937] Example 59: Synthesis of 4-cyano-5-(morpholin-4-yl)-3-[(4-oxoquinazolin-3(4H)-yl)methyl]thiophene-2-carboxylic acid (Compound 294)



[00938] Step 1: Methyl 4-cyano-5-(morpholin-4-yl)-3-[(4-oxoquinazolin-3(4H)-yl)methyl]thiophene-2-carboxylate

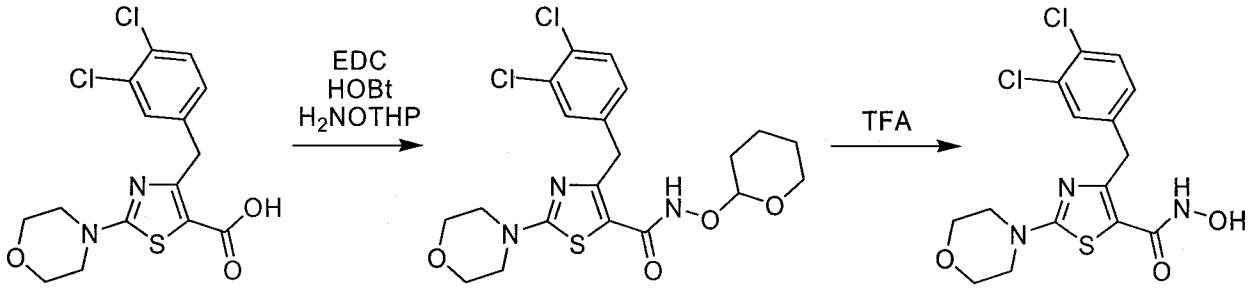
[00939] Under N_2 atmosphere Sodium hydride (23.0 mg, 0.910 mmol) was suspended in anhydrous N,N-Dimethylformamide (3.0 mL, 39 mmol), cooled with ice bath and stirred for 10 min. 4-hydroxyquinazoline (0.120 g, 0.821 mmol) was added and the clear solution was stirred at r.t. for 10 min, cooled with ice bath. Mmethyl 3-(bromomethyl)-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylate (0.203 g, 0.588 mmol) was added and the reddish-brown solution was stirred with cooling for 40 min. The mixture was quenched with saturated NH4Cl aqueous solution, extracted with EtOAc. The EtOAc solution was washed with water (3x) then brine, dried over Na_2SO_4, filtered, rotavaped to give a crude solid. Chromatograph in a silica gel column using MeOH/DCM (0/100 to 5/95) afforded a solid product (0.211 g, yield 87.4%). LC/MS: (FA) ES^+ 411. ^1H NMR (400MHz, *d*-chloroform) δ 8.30 (m, 1H), 8.26 (s, 1H),7.68-7.76 (m, 2H), 7.45-7.49 (m, 1H), 5.43 (s, 2H), 3.83-3.85 (m, 4H), 3.82 (s, 3H), 3.59-3.62 (m, 4H).

[00940] Step 2: 4-Cyano-5-(morpholin- 4-yl)-3-[(4-oxoquinazolin- 3(4H)-yl)methyl]thiophene- 2-carboxylic acid sodium salt

[00941] Methyl 4-cyano-5-(morpholin-4-yl)-3-[(4-oxoquinazolin-3(4H)-yl)methyl]thiophene-2-carboxylate (0.139 g, 0.339 mmol) was disolved in Tetrahydrofuran (15.0 mL), Water (2.0 mL) and Methanol (5.0 mL). 1.00 M of Sodium hydroxide in Water (1.0 mL, 1.0 mmol) was added and the homogeneous solution was stirred at room temperature for 24 hours. The solution was concentrated in rotavapor to give a white crude solid, dissolved in H2O/MEOH (1/10, ~ 20 mL) and concentrated in rotavapor until a white suspension (~ 2 mL volumn). The suspension was filtered to collect the solid, dried in lyopholizer to give a white solid product (0.132 g, yield 92.2 %). LC/MS: (FA) ES^+ 397; ES^- 395.

^{1}H NMR (400MHz, *d4*-methanol) δ 8.37 (s, 1H), 8.22 (d, J = 8.03 Hz, 1H),7.78-7.82 (m, 1H), 7.65 (d, J = 7.28 Hz, 1H), 7.51-7.55 (m, 1H), 5.99 (s, 2H), 3.78-3.81 (m, 4H), 3.47-3.50 (m, 4H).

[00942] Example 60: Synthesis of 4-(3,4-dichlorobenzyl)-N-hydroxy-2-(morpholin-4-yl)-1,3-thiazole-5-carboxamide (Compound 298)



[00943] Step1: To a suspension of 4-(3,4-dichlorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylic acid•Na(125 mg, 0.316 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (72.8 mg, 0.380 mmol), and 1-hydroxybenzotriazole (51.3 mg, 0.380 mmol) in N,N-dimethylformamide (1.50 mL) was added O-(tetrahydropyran-2-yl)hydroxylamine (55.6 mg, 0.474 mmol). The reaction was stirred at rt for 15 hrs. The mixture was distributed between water and EtOAc, and the aqueous layer was extracted with EtOAc(x2). The combined organic layer was washed with $NaHCO_3$(aq) saturated solution and 10% LiCl(aq) soln(x2), dried over Na_2SO_4, and concentrated to provide 4-(3,4-dichlorobenzyl)-2-(morpholin-4-yl)-N-(tetrahydro-2H-pyran-2-yloxy)-1,3-thiazole-5-carboxamide as a white solid (153 mg, quantitative). LCMS: (AA) ES+ 472, 474, 476; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.43 (d, *J* = 1.9 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.26 – 7.17 (m, 1H), 5.01 – 4.89 (d, *J* = 2.8 Hz, 1H), 4.31 – 4.21 (m, 2H), 3.96 – 3.86 (td, *J* = 10.4, 9.1, 2.8 Hz, 1H), 3.80 – 3.70 (t, *J* = 4.9 Hz, 4H), 3.66 – 3.56 (m, 1H), 3.51 – 3.42 (t, *J* = 4.9 Hz, 4H), 1.90 – 1.73 (m, 3H), 1.69 – 1.49 (m, 3H).

[00944] Step2: To a solution of 4-(3,4-dichlorobenzyl)-2-(morpholin-4-yl)-N-(tetrahydro-2H-pyran-2-yloxy)-1,3-thiazole-5-carboxamide (153 mg, 0.324 mmol) in methylene chloride (1.50 mL) was added trifluoroacetic Acid (1.50 mL, 19.5 mmol). The reaction was stirred at rt for 12 hrs. The resulting solution was concentrated and distributed between $NaHCO_3$(aq) saturated solution and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2(x2). The combined org layer was washed with water, dried, and concentrated. Purification on a silica gel column (gradient elution, 0-8% MeOH/CH_2Cl_2) provided 4-(3,4-dichlorobenzyl)-N-hydroxy-2-(morpholin-4-yl)-1,3-thiazole-5-carboxamide as a yellow solid (53 mg, 42.1% yield). LCMS: (AA) ES+ 388, 390,

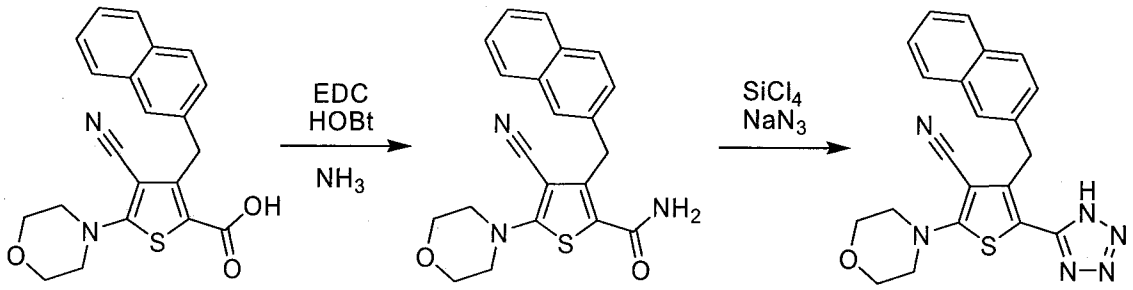
392; ^{1}H NMR (400 MHz, MeOD) δ 7.47 – 7.41 (d, J = 1.8 Hz, 1H), 7.38 – 7.29 (d, J = 8.3 Hz, 1H), 7.25 – 7.14 (dd, J = 8.3, 1.9 Hz, 1H), 4.28 – 4.21 (s, 2H), 3.79 – 3.71 (t, J = 4.9 Hz, 4H), 3.50 – 3.43 (t, J = 4.9 Hz, 4H), 3.33 – 3.27 (t, J = 1.6 Hz, 1H).

[00945] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 60.

334	LC/MS: (AA) ES+ 354

[00946]

[00947] Example 61: Synthesis of 2-(morpholin-4-yl)-4-(2-naphthylmethyl)-5-(1H-tetrazol-5-yl)thiophene-3-carbonitrile (Compound 316)

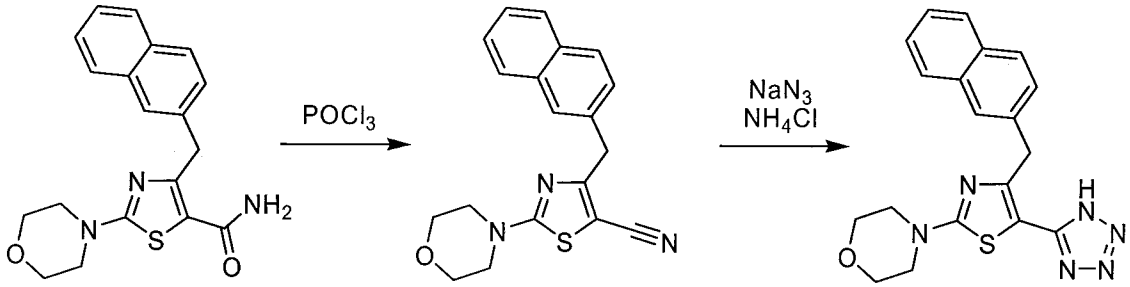


[00948] **Step1**: To a mixture of 4-cyano-5-morpholin-4-yl-3-(2-naphthylmethyl)thiophene-2-carboxylic acid•Na(255 mg, 0.637 mmol) in N,N-dimethylformamide (6.00 mL) was added 1-hydroxybenzotriazole hydrate (117 mg, 0.764 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (146 mg, 0.764 mmol), and 0.500 M of ammonia in 1,4-dioxane(3.18 mL, 1.59 mmol). The reaction was vigorously stirred at rt for 5 hrs. The mixture was distributed between brine and EtOAc, and the aqueous layer was extracted with EtOAc(x2). The combined organic layers were washed with 10% LiCl(aq) solution (x2), dried, and concentrated to provide 4-cyano-5-(morpholin-4-yl)-3-(2-naphthylmethyl)thiophene-2-carboxamide (Compound 327) as a white solid (224 mg, 93.2% yield). LCMS: (AA) ES+ 378; ^{1}H NMR (400 MHz, DMSO) δ 7.89 – 7.76 (td, J = 11.0, 6.6 Hz, 3H), 7.68 – 7.62 (s, 1H), 7.51 – 7.44 (td, J = 6.8, 6.0, 3.7 Hz, 3H), 7.43 – 7.34 (m, 1H), 4.50 – 4.42 (s, 2H), 3.78 – 3.69 (t, J = 4.9 Hz, 4H), 3.50 – 3.40 (t, J = 4.9 Hz, 4H).

[00949] **Step2**: To a mixture of sodium azide (153 mg, 2.35 mmol) in acetonitrile (2.50 mL) in a 20 mL microwave tube was added silicon(IV) chloride (89.9 uL, 0.783 mmol). The mixture was stirred at rt under an atmosphere of Nitrogen for 20 min, then 4-cyano-5-(morpholin-4-yl)-3-(2-naphthylmethyl)thiophene-2-carboxamide (197 mg, 0.522 mmol) was added. The tube was sealed and the reaction was heated to 90 °C for 12 hrs. The mixture was cooled and distributed

between water and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was washed with brine, dried, and concentrated to provide a purple syrup. Purification on HPLC (reverse phase, AA) provided 2-(morpholin-4-yl)-4-(2-naphthylmethyl)-5-(1H-tetrazol-5-yl)thiophene-3-carbonitrile as a yellow solid (44 mg, 20.9% yield). LCMS: (AA) ES+ 403; ^{1}H NMR (400 MHz, MeOD) δ 7.78 – 7.73 (m, 1H), 7.73 – 7.67 (d, J = 7.8 Hz, 2H), 7.67 – 7.61 (s, 1H), 7.42 – 7.36 (m, 2H), 7.36 – 7.30 (m, 1H), 4.63 – 4.57 (s, 2H), 3.85 – 3.76 (t, J = 4.9 Hz, 4H), 3.57 – 3.48 (t, J = 4.8 Hz, 4H).

[00950] Example 62: Synthesis of 4-[4-(2-naphthylmethyl)-5-(1H-tetrazol-5-yl)-1,3-thiazol-2-yl]morpholine (Compound 360)



[00951] Step1: A mixture of 2-(morpholin-4-yl)-4-(2-naphthylmethyl)-1,3-thiazole-5-carboxamide (229 mg, 0.648 mmol) (for amide coupling, see example 61 – step 1) and phosphoryl chloride (4.00 mL, 42.9 mmol) was stirred at 80 °C for 30 min. The reaction slowly turned homogeneous. The resulting solution was concentrated under reduced pressure and carefully quenched with 1N NaOH solution at 0 °C. The resulting mixture was distributed between 1N NaOH solution and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layer was dried and concentrated to provide 2-(morpholin-4-yl)-4-(2-naphthylmethyl)-1,3-thiazole-5-carbonitrile as a yellow solid (213 mg, 98.0% yield). LCMS: (AA) ES+ 336; ^{1}H NMR (400 MHz, DMSO) δ 7.90 – 7.83 (dd, J = 9.0, 1.9 Hz, 3H), 7.80 – 7.72 (s, 1H), 7.53 – 7.46 (m, 2H), 7.46 – 7.38 (m, 1H), 4.18 – 4.09 (s, 2H), 3.70 – 3.60 (t, J = 4.9 Hz, 4H), 3.51 – 3.41 (t, J = 4.9 Hz, 4H).

[00952] Step2: To a solution of 2-(morpholin-4-yl)-4-(2-naphthylmethyl)-1,3-thiazole-5-carbonitrile (213 mg, 0.635 mmol) in N,N-dimethylformamide (3.00 mL) was added sodium azide (61.9 mg, 0.952 mmol) and ammonium chloride (102 mg, 1.90 mmol). The mixture was heated to 100 °C and stirred for 24 hrs. The resulting mixture was cooled to rt and distributed between water and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was washed with 10% LiCl(aq) solution (x2), dried, and concentrated. Purification

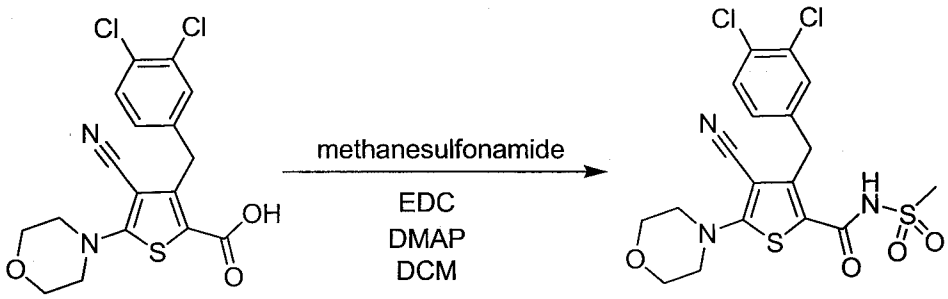
on HPLC (reverse phase, AA) provided 4-[4-(2-naphthylmethyl)-5-(1H-tetrazol-5-yl)-1,3-thiazol-2-yl]morpholine as a yellow solid (105 mg, 43.7% yield). LCMS: (AA) ES+ 379; ^{1}H NMR (400 MHz, MeOD) δ 7.79 – 7.61 (m, 4H), 7.43 – 7.31 (m, 3H), 4.57 – 4.45 (s, 2H), 3.82 – 3.68 (t, J = 4.9 Hz, 4H), 3.53 – 3.43 (t, J = 4.9 Hz, 4H).

[00953] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 62.

356	LC/MS: (AA) ES+ 378

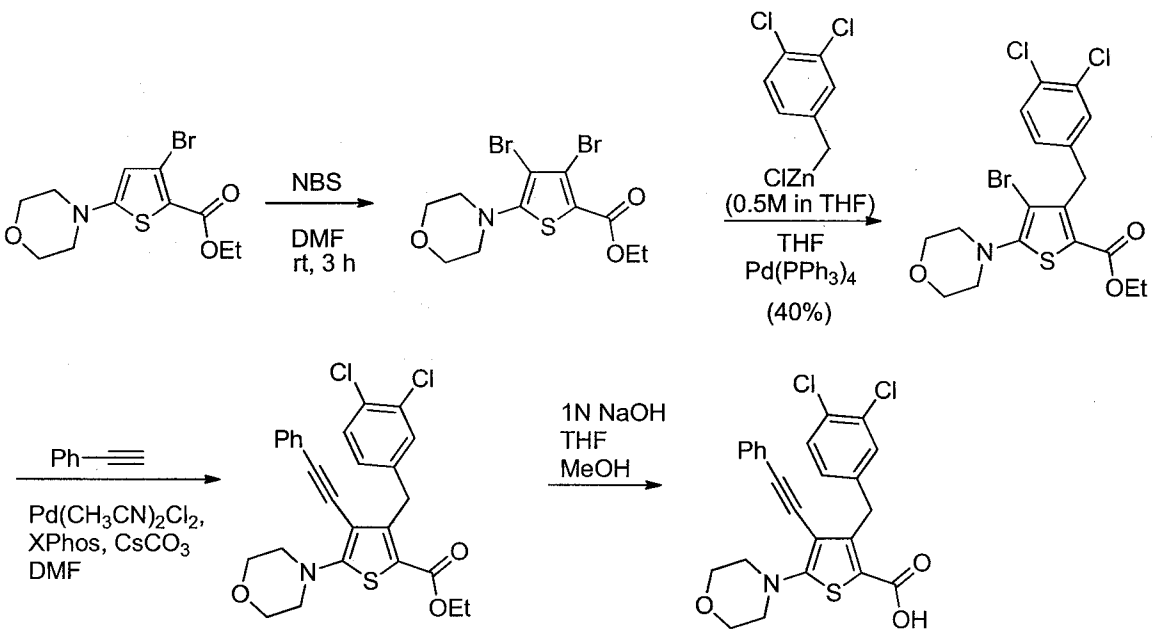
[00954]

[00955] Example 63: Synthesis of 4-cyano-3-(3,4-dichlorobenzyl)-N-(methylsulfonyl)-5-morpholinothiophene-2-carboxamide (Compound 352)



[00956] To a mixture of 4-cyano-3-(3,4-dichlorobenzyl)-5-morpholinothiophene-2-carboxylic acid (291 mg, 0.732 mmol), in DCM (5.0 mL) was added methanesulfonamide (87.1 mg, 0.916 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (176 mg, 0.916 mmol), and *N,N*-dimethylaminopyridine (103 mg, 0.842 mmol) and the resulting solution was stirred at room temperature overnight. The reaction was diluted with DCM (10 mL), 1N HCl (3 mL) and with water (3 mL). The organic layer was dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→20/80) to give 250 mg of crude product. This material was purified by preparative reverse phase chromatography to give 70 mg (20 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 474, 476. ^{1}H NMR (400 MHz, MeOH-d_4) δ: 7.45 (d, 1H, J = 2.0 Hz)), 7.38 (d, 1H, J = 8.4 Hz), 7.25 (dd, 1H, J = 8.0, 2.0 Hz), 4.38 (s, 2H), 3.82-3.80 (m, 4H), 3.57-3.55 (m, 4H), 3.18 (s, 3H).

[00957] Example 64: Synthesis of 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)thiophene-2- carboxylic acid (Compound 296).



[00958] **Step 1:** Ethyl 3,4-dibromo-5-(morpholin-4-yl)thiophene-2-carboxylate.

[00959] To a degassed solution of ethyl 3-bromo-5-morpholin-4-ylthiophene-2-carboxylate (0.688 g, 2.15 mmol) in DMF (14 mL, 180 mmol) was added N-bromosuccinimide (0.7648 g, 4.297 mmol) dropwise as a solution in degassed DMF (4.1 mL, 52 mmol). The mixture was wrapped in foil to protect from ambient light, and the reaction was stirred under argon at room temperature for 2 hours. The reaction mixture was quenched via addition of 10% sodium thiosulfate solution (10 mL) and then diluted with EtOAc (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (eluent: 0-25% EtOAc:hexane) afforded ethyl 3,4-dibromo-5-(morpholin-4-yl)thiophene-2-carboxylate (593 mg, yield 69%). LCMS: (FA) ES+ 398, 400, 402; ^{1}H NMR (400 MHz, DMSO) δ 4.26 (q, J = 7.1 Hz, 2H), 3.75 (dd, J = 5.5, 3.8 Hz, 4H), 3.24 – 3.10 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H).

[00960] **Step 2:** Ethyl 4-bromo-3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)thiophene-2-carboxylate.

[00961] A sealable reaction vessel containing a suspension of ethyl 3,4-dibromo-5-(morpholin-4-yl)thiophene-2-carboxylate (0.560 g, 1.40 mmol), 0.500 M 3,4-dichlorobenzylzinc chloride in THF (3.368 mL, 1.684 mmol) and THF (2.06 mL, 25.4 mmol) was purged via vacuum/backfilling with argon. To this suspension was added tetrakis(triphenylphosphine)palladium(0) (81.07 mg, 0.07016 mmol), the vial was capped, and the resulting black suspension was stirred at 95 °C overnight. The reaction mixture was adsorbed to celite in vacuo, and the solid thus obtained was purified via column chromatography (eluent: 0-15% EtOAc:hexane) to afford ethyl 4-bromo-3-(3,4-dichlorobenzyl)-5-(morpholin-4-

yl)thiophene-2-carboxylate (323 mg, 50%). LCMS: (FA) ES+ 478, 480, 482; ^{1}H NMR (400 MHz, DMSO) δ 7.53 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.07 (dd, J = 8.3, 2.1 Hz, 1H), 4.36 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.75 – 3.70 (m, 4H), 3.17 – 3.12 (m, 4H), 1.22 (t, J = 7.1 Hz, 3H).

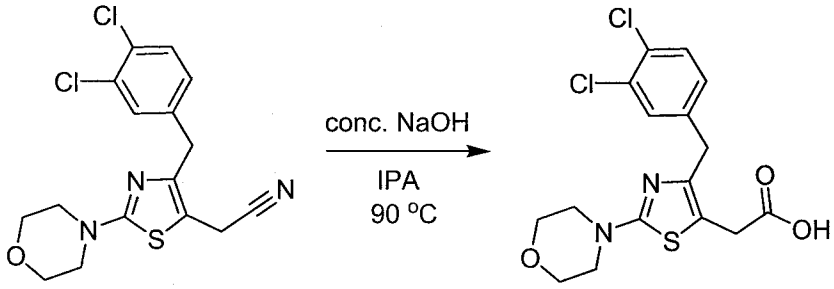
[00962] **Step 3:** Ethyl 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)-thiophene-2-carboxylate.

[00963] To a suspension of ethyl 4-bromo-3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)thiophene-2-carboxylate (0.125 g, 0.000222 mol), XPhos (0.0172 g, 0.0000362 mol), CsCO3 (0.199 g, 0.000612 mol) and phenylacetylene (0.146 mL, 0.00133 mol) in DMF (1.2 mL, 0.015 mol) was added bis(acetonitrile)palladium(II) chloride (0.00288 g, 0.0000111 mol) and the mixture was heated at 50 °C overnight. The reaction mixture was diluted with EtOAc (30 mL) and water (15 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 15mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified using a dry load on a silica gel column (eluent: 0-30% EtOAc:hexane), affording ethyl 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)thiophene-2-carboxylate (45 mg, 40% yield). LCMS: (FA) ES+ 500, 501, 502; ^{1}H NMR (400 MHz, DMSO) δ 7.55 – 7.51 (m, 2H), 7.43 – 7.37 (m, 5H), 7.20 (dd, J = 8.3, 2.0 Hz, 1H), 4.38 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.79 – 3.74 (m, 4H), 3.57 – 3.52 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H).

[00964] **Step 4:** 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)-thiophene-2-carboxylic acid.

[00965] To a suspension of ethyl 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)thiophene-2-carboxylate (0.041 g, 0.082 mmol in THF (2.00 mL, 24.6 mmol) and methanol (0.37 mL, 9.1 mmol) was added 1.000 M of sodium hydroxide in water (1.684 mL, 1.684 mmol) and the resulting biphasic mixture was stirred at room temp for 2 days. The pH was carefully adjusted to 3.0 via addition of 1N HCl (monitored in real time with a pH meter), and the reaction mixture was transferred to a separatory funnel. The mixture was diluted with EtOAc (40 mL) and water (15 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine, then dried over Na_2SO_4, filtered, and concentrated. Column chromatography (eluent: 0-5% MeOH:DCM) afforded 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)thiophene-2-carboxylic acid (30 mg, 78% yield). LCMS: (FA) ES+ 472, 473, 474; ^{1}H NMR (400 MHz, DMSO) δ 12.92 (s, 1H), 7.55 – 7.50 (m, 2H), 7.43 – 7.34 (m, 5H), 7.21 (dd, J = 8.3, 2.0 Hz, 1H), 4.39 (s, 2H), 3.81 – 3.68 (m, 4H), 3.56 – 3.42 (m, 4H).

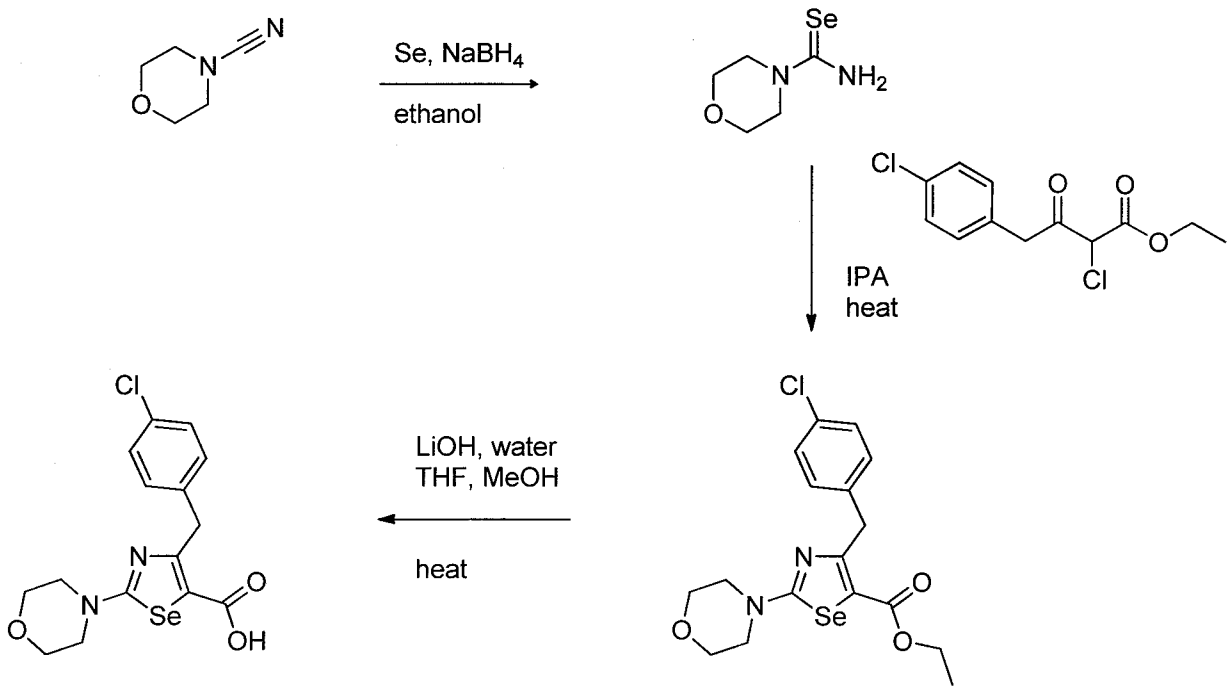
[00966] **Example 65: Synthesis of 2-(4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)acetic acid (Compound 348)**



from example 65 above

[00967] To a solution of 2-(4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)acetonitrile (165 mg, 0.448 mmol) in IPA (4.88 mL) was added 50% aqueous NaOH (1.68 mL, 44.8 mmol) and the resulting solution was heated to 90 degrees for 3 hours.The reaction was cooled and concentrated in vacuo. The residue was acidified with 1 N HCl and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→20/80) to give 120 mg of product. This material was purified by preparative reverse phase chromatography to give 16 mg (9 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 387, 389. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.49 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 2.0 Hz), 7.21 (dd, 1H, J = 8.0, 2.0 Hz), 3.78 (s, 2H), 3.67 (s, 2H), 3.66-3.63 (m, 4H), 3.26-3.24 (m, 4H).

[00968] Example 66: Synthesis of 4-(4-chlorobenzyl)-2-morpholino-1,3-selenazole-5-carboxylic acid (Compound 370)



[00969] Step 1: Morpholine-4-carboselenoamide

[00970] In a round bottomed flask equipped with a stir bar were added selenium metal (4.00 g, 49.4 mmol) and ethanol (50 mL). The mixture was cooled in an ice bath and stirred under a nitrogen atmosphere while sodium tetrahydroborate (2.01 g, 53.1 mmol) was slowly added. Gas was evolved and the selenium slowly dissolved. After gas evolution had ceased, 4-morpholinecarbonitrile (2.77 g, 24.7 mmol) was slowly added followed by pyridine hydrochloride (11.4 g, 98.7 mmol). The resulting dark mixture was stirred overnight at room temperature.The grayish reaction mixture was quenched with water (~250 mL) and the mixture was stirred briefly then transferred to a separatory funnel. The mixture was extracted with dichloromethane (3X). The extracts were combined and dried over sodium sulfate. The insolubles were filtered off and the filtrate was evaporated to leave a light pink solid which was stirred with water then filtered. The collected solid was washed with ethyl acetate and the washings were combined then evaporated to leave 80 mg (2% yield) product as a light pink solid. LC/MS (FA) ES+ 195. ^{1}H NMR (400 MHz, DMSO) δ 8.15 - 7.71 (br s, 2H), 3.94 - 3.61 (br s, 4H), 3.60 - 3.51 (t, J = 4.9 Hz, 4H).

[00971] Step 2: Ethyl 4-(4-chlorobenzyl)-2-morpholino-1,3-selenazole-5-carboxylate

[00972] In a round bottomed flask were placed ethyl 2-chloro-4-(4-chlorophenyl)-3-oxobutanoate (84.4 mg, 0.3069 mmol), isopropyl alcohol (5 mL), and morpholine-4-carboselenoamide (80.0 mg, 0.414 mmol). The resulting mixture was brought to reflux under an atmosphere of nitrogen (all solids dissolved to give a clear pale pink solution). After ~1 hour reflux, TLC analysis indicated that all starting materials had been consumed with the production of one major product. The reaction was allowed to cool to room temperature and stir overnight. The solvent was removed on the rotovap then the residue was dissolved in minimal dichloromethane and purified by column chromatography on silica gel (gradient 100% hexane to 35% ethyl acetate) to afford 35 mg (28% yield) product as a white solid. LC/MS (FA) ES+ 413/415/417. ^{1}H NMR (400 MHz, DMSO) δ 7.37 - 7.23 (m, 4H), 4.25 - 4.14 (m, 4H), 3.72 - 3.62 (t, J = 4.9 Hz, 4H), 3.50 - 3.41 (t, J = 4.8 Hz, 4H), 1.27 - 1.20 (t, J = 7.1 Hz, 3H).

[00973] Step 3: 4-(4-chlorobenzyl)-2-morpholino-1,3-selenazole-5-carboxylic acid

[00974] The ethyl 4-(4-chlorobenzyl)-2-(morpholin-4-yl)-1,3-selenazole-5-carboxylate (35.0 mg, 0.0846 mmol) was placed in a round bottomed flask equipped with a stirbar. Tetrahydrofuran (1.00 mL) and methanol (0.1 mL) were added and the mixture was stirred to give a light yellow solution. A solution of lithium hydroxide in water (2.0 M, 0.423 mL, 0.846 mmol) was added in a single portion, and the resulting mixture was stirred under an atmosphere of nitrogen at room temperature overnight. LCMS analysis of the reaction indicated that starting material still remained; only a small amount of it had been hydrolyzed to the product. Additional tetrahydrofuran (2 mL) and lithium hydroxide in water (2.0 M, 0.423 mL, 0.846 mmol) were added and the reaction was heated overnight at 50°C under an atmosphere of nitrogen. LCMS analysis indicated that the reaction was 90% complete. The reaction was heated at

60° C for a further 8 hours. LCMS analysis indicated complete hydrolysis. The reaction was cooled to room temperature, diluted with 10 ml saline, and acidified with dilute acetic acid with good stirring. A white precipitate formed which became granular with stirring. The product was isolated on a fritted funnel, washed with water, and dried at 40° C overnight to yield 29.2 mg (89% yield) product as a white powder. LC/MS (FA) ES+ 385/387/389. ^{1}H NMR (400 MHz, DMSO) δ 12.73 – 12.44 (br s, 1H), 7.36 – 7.24 (m, 4H), 4.26 – 4.18 (s, 2H), 3.74 – 3.63 (t, J = 4.8 Hz, 4H), 3.49 – 3.39 (t, J = 4.7 Hz, 4H).

[00975] Formulation Example 1 (amount per tablet)

(1) Compound obtained in Example 1	10.0 mg
(2) Lactose	60.0 mg
(3) Corn starch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

[00976] A mixture of 10.0 mg of the compound obtained in Example 1, 60.0 mg of lactose and 35.0 mg of corn starch is granulated through a 1 mm-mesh sieve using 0.03 ml of a 10% by weight aqueous solution of gelatin (3.0 mg of gelatin), after which the granules are dried at 40°C and filtered again. The granules obtained are mixed with 2.0 mg of magnesium stearate and compressed. The core tablets obtained are coated with a sugar coat comprising a suspension of sucrose, titanium dioxide, talc and gum arabic and polished with beeswax to yield sugar-coated tablets.

[00977] Formulation Example 2 (dose per tablet)

(1) Compound obtained in Example 1	10.0 mg
(2) Lactose	70.0 mg
(3) Corn starch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

[00978] 10.0 mg of the compound obtained in Example 1 and 3.0 mg of magnesium stearate are granulated using 0.07 ml of an aqueous solution of soluble starch (7.0 mg of soluble starch), after which these granules are dried and mixed with 70.0 mg of lactose and 50.0 mg of corn starch. This mixture is compressed to yield tablets.

[00979] BIOLOGICAL DATA:

[00980] PI3K and VPS34 Enzyme Assays

[00981] Cloning, expression, and purification of PI3Ks and VPS34

[00982] The catalytic subunits of PI3Ks are cloned into either pDEST8(p110 alpha) or pDEST10(p110beta, p110delta, and p110gamma) as N-terminal His tagged fusion proteins using the Gateway system (Invitrogen, catalog# 11804-010 for pDEST8 and 11806-015 for pDEST10). The sequences are verified before recombinant protein expression using the Baculovirus Expression System with Gateway® Technology. The accession numbers for the subunits are as follows:

p110 alpha (GB:U79143)

p110beta (GB:S67334)

p110delta (GB: U86453)

p110gamma (GB: X83368)

[00983] The regulatory subunits of PI3Ks are cloned into pDEST8 as un-tagged protein using the Gateway system (Catalog#11804-010). The sequences are verified before recombinant protein expression using the Baculovirus Expression System with Gateway® Technology. The accession numbers for the subunits are as following:

p85 alpha (GB: BC030815)

p101(GB: AB028925)

[00984] VPS34 (accession number GB:BC033004) is cloned into pDEST20-Thombin as N-terminal GST tagged fusion proteins using the Gateway system (Invitrogen, catalog# 11804-013). The sequences are verified before recombinant protein expression using the Baculovirus Expression System with Gateway® Technology.

[00985] For expression of the p110 complexes, the p85 (MOI of 4) is co-infected with p110 alpha, beta, and delta respectively (1MOI) in SF9 cells and harvested at 60 hours post co-infection. P110 gamma was infected at 1 MOI and harvested at 60 hours post infection.

[00986] For purification, PI3Ks are purified by Ni-NTA Agarose (Qiagen #30250) followed by Mono Q 10/100 GL (Ge Healthcare #17-5167-01). VPS34 is purified by Glutathione Sepharose 4 Fast Flow (GE Healthcare #17-5132-03) followed by HiTrap Q (GE Healthcare #17-1153-01).

[00987] For expression VPS34 was infected at 1MOI in SF9 cells and harvested 72 hours post infection.

[00988] For purification, VPS34 is purified by Glutathione Sepharose 4 Fast Flow (GE Healthcare #17-5132-03) followed by HiTrap Q (GE Healthcare #17-1153-01).

[00989] PI3K and VPS34 Assay Conditions

[00990] 1) Human PI3K alpha enzyme assay method

[00991] 0.5uL compounds in DMSO are added to wells of a 384 well microtitre plate (Corning 3575). At room temperature: 10ul PI3K reaction buffer (50 mM Hepes, 5mM DTT, 150mM NaCl, 10mM beta-glycerophosphate, 10mM MgCl2, 0.25mM sodium cholate and 0.001% CHAPS, pH 7.00) containing ATP (25uM, Promega) is added followed immediately by 10ul PI3K reaction buffer containing di-C8 PI(4,5)P2 (3.5uM, CellSignals) and PI3Kalpha (0.4875nM, Millennium Protein Sciences Group) and the mixture is incubated with shaking at room temperature for 30 minutes. Then 5ul PI3K stop mix (50mM Hepes, 5mM DTT, 150 mM NaCl, 0.01% Tween-20, 15 mM EDTA and 25nM biotin-PI(3,4,5)P3 (Echelon) is added to quench the reaction followed immediately by addition of 5ul HTRF detection mix (50mM Hepes, 5mM DTT, 150 mM NaCl, 0.01% Tween-20, 40mM KF, 10nM GST:GRP-1 PH domain (Millennium Protein Sciences Group), 15nM Streptavidin-XL (CisBio) and 0.375nM anti-GST Eu++ antibody (CisBio) at pH 7.00). The plates are then incubated for 1 hour at room temperature with shaking and then read on a BMG PheraStar Plus reader.

[00992] 2) Human PI3K beta, delta and gamma isoforms are tested using the procedure described for PI3K alpha above but with the following changes: PI3K beta (5.25nM), PI3K delta (0.75nM) and PI3K gamma (5nM). All isoforms supplied by Millennium Protein Science Group.

[00993] 3) VPS34 is assayed using Adapta ™ Universal Kinase Assay Kit (Invitrogen).

[00994] 4) Human VPS34 enzyme assay method

[00995] 100nL compounds in DMSO are added to wells of a 384 well microtitre plate (Greiner 780076). At room temperature: 5ul VPS34 reaction buffer (Invitrogen Assay Buffer Q (diluted 1 in 5 with nanopure water) plus 2mM DTT and 2mM MnCl2) containing ATP (20uM, Promega) and 200uM PI-PS substrate (Invitrogen PV5122) is added followed immediately by 5ul VPS34 reaction buffer (as above) containing VPS34 (5nM, Millennium Protein Sciences Group) and the mixture is incubated with shaking at room temperature for 1 hour. Then 5ul VPS34 stop-detect mix (as per Invitrogen Adapta Assay kit (PV5009) instructions (contains kinase quench buffer, TR-FRET buffer, Adapta Eu anti-ADP antibody and Alexa Fluor 647 ADP tracer)) is added to quench the reaction. The plates are then incubated for 30 minutes at room temperature with shaking and then read on a BMG PheraStar Plus reader.

[00996] For the assay methods described above, test compound percent inhibition, at various concentrations, is calculated relative to control (DMSO and EDTA) treated samples. Compound concentration versus percent inhibition curves are fitted to generate IC_{50} values. One skilled in the art will appreciate that the values generated either as percentage inhibition at a single concentration or IC_{50} values are subject to experimental variation.

[00997] **PI3K Cell Assays**

[00998] **1) In-Cell Western Assay**

[00999] The pSer473 AKT LI-COR In-Cell Western Assay is a quantitative immunofluorescent assay that measures phosphorylation of serine 473 AKT (pSer473 AKT) in WM266.4 and SKOV3 tumor cell lines grown in cell culture.

[001000] WM266.4 cells are propagated in Minimum Essential Media (MEM) (Invitrogen) containing L-glutamine, 10% Fetal Bovine Serum, 1 mM MEM Sodium Pyruvate, and 0.1 mM MEM Non-Essential Amino Acids and SKOV3 cells are propagated in McCoy's 5A Media (modified) (Invitrogen) containing L-Glutamine and 10% Fetal Bovine Serum. Both cell lines are kept in a humidified chamber at 37°C with 5% CO_2. For the pSer473 AKT LI-COR In-Cell Western Assay, 1.5 x 10^4 WM266.4 and 1.5 x 10^4 SKOV3 cells are cultured in 100 µl of media per well in tissue culture-treated black-walled, clear bottom Optilux 96-well plates (BD Biosciences) for 16-20 hours. Prior to addition of compounds, cell media is removed and replaced with 75 µl of fresh media. Test compounds in DMSO are diluted 1:100 in media. The diluted test compounds are added to the cells (25 µl per well) in 3-fold dilutions with a final concentration range of 0.0015 to 10 µM. The cells are incubated for 2 hours in a humidified chamber at 37°C with 5% CO_2. Immediately following compound incubation, all liquid is removed from the wells and cells are fixed with 4% paraformaldehyde in PBS (150 µl per well) for 20 minutes at room temperature. The paraformaldehyde solution is removed from wells and the cells are permeabilized with 200 µl 0.1% Triton X-100 in PBS per well for 10 min x 3 at room temperature. After removal of PBS + 0.1% Triton X-100, 150 µl Odyssey blocking buffer (LI-COR Biosciences) is added to each well and plates are incubated at room temperature for 1.5 h. Blocking buffer is removed from the wells and primary antibodies (Phospho-AKT (Ser473) (D9E) XP™ Rabbit mAb and AKT (pan) (40D4) Mouse mAb, Cell Signaling Technology) diluted in Odyssey blocking buffer are added (50 µl per well). Plates are incubated at 4°C overnight. The cells are washed for 20 min x 3 with PBS + 0.1% Tween-20 (200 µl per well). Secondary antibodies (IRDye 680 Goat anti-Rabbit IgG (H+L) and IRDye 800CW Goat anti-Mouse IgG (H+L), LI-COR Biosciences) are diluted in Odyssey blocking buffer and added to wells (50 µl per well) followed by a 1 h incubation at room temperature, protected from light. Cells are washed for 20 min x 3 with PBS + 0.1% Tween-20 (200 µl per well). Wash buffer is completely removed from wells after last wash, plates are protected from light until scanned and analyzed with the Odyssey Infrared Imaging System (LI-COR Biosciences). Both pS473 AKT and AKT are simultaneously visualized with the 680 nm fluorophore indicated by a red color and the 800 nm fluorophore indicated by a green color. Relative fluorescence units derived from the scans allow for quantitative analyses of both labeled proteins and the ratio of pS473 AKT to AKT is calculated. Concentration response curves are generated by plotting the average ratios of PI3K inhibitor-treated samples relative to DMSO-treated controls to determine percent change in expression of pS473 AKT, and percentage inhibition values at a single concentration or growth inhibition (IC_{50}) values are determined from those curves. One skilled in the art

will appreciate that the values generated either as percentage inhibition at a single concentration or IC_{50} values are subject to experimental variation.

[001001] 2) ATPlite Viability Assay

[001002] The ATPLite™ Assay (Perkin-Elmer) measures cellular adenosine-triphosphate (ATP) through the generation of a luminescent signal formed from the ATP-dependent enzyme firefly luciferase. The luminescent signal intensity can be used as a measure of cellular proliferation, and can be used to assess the anti-proliferative effects of PI3K inhibitors.

[001003] WM266.4 cells propagated in Minimum Essential Media (MEM) (Invitrogen) containing L-Glutamine, 10% Fetal Bovine Serum, 1 mM MEM Sodium Pyruvate, and 0.1 mM MEM Non-Essential Amino Acids are cultured in 384-well tissue culture-treated Black/Clear plates (Falcon) at 1 x 10^3 cells per well in a volume of 75 µl in a humidified chamber at 37°C with 5% CO_2 for 24 h. Test compounds (2 µl in 100% DMSO) are diluted in 95 µl of cell culture media. The diluted test compounds are added (8 µl per well) to 384-well plates. Final concentration range of 3-fold serial dilution of compounds is 0.001 to 20 µM. Plates are incubated for 72 h in a humidified chamber at 37°C with 5% CO_2. One control plate without compound addition is processed at the start of the 72 h incubation as a "Time Zero" reading for quantitative evaluation of cell viability at start of assay. After 72 h, all but 25 µl of cell culture media is removed from each well, followed by the addition of 25 µl of ATPlite 1step reagent (Perkin Elmer) to each well. Luminescence is measured on a LEADSeeker Luminescence Counter (GE Healthcare Life Sciences). Concentration response curves are generated by calculating the luminescence decrease in test compound-treated samples relative to DMSO-treated controls, and percentage inhibition values at a single concentration or growth inhibition (IC_{50}) values are determined from the curves. One skilled in the art will appreciate that the values generated either as percentage inhibition at a single concentration or IC_{50} values are subject to experimental variation.

[001004] Vps34 Cell Assays

[001005] 1) FYVE domain redistribution assay

[001006] The FYVE domain redistribution assay monitors translocation of EGFP-2XFYVE from its initial location bound to (PtdIns(3)P) in early endosomes to the cytoplasm in response to test compounds. Recombinant U2OS cells stable expressing the FYVE finger from the human homologue of the hepatocyte growth factor-regulated tyrosine kinase substrate Hrs, duplicated in tanden (GenBank Acc. NM_004712) and fused to the C-terminus of enhanced green fluorescent protein (EGFP). U2OS cells are adherent epithelial cells derived from human osteosarcoma. Expression of EGFP-2X-FYVE is controlled by a standard CMV promoter and continous expression is maintained by addition of geneticin to the culture medium. Localization of the fusion protein within the cells is imaged on the Evotec Technologies

OPERA Confocal Imager and Integrated Spot Signal Per Cellular Signal is quantified using Acapella software. Using this information, percentage inhibition values at a single concentration or IC_{50} values for inhibitors can be determined.

[001007] U2OS EGFP-2XFYVE cells are propagated in Dulbecco's Modified Eagle Media High glucose(D-MEM) (Invitrogen cat. 11995) containing 10% Fetal Bovine Serum (HyClone cat. SH30071.02) and 0.5mg/ml Geneticin (Invitrogen) and kept in a humidified chamber at 37°C with 5% CO_2. 8 x 10^3 cells are cultured in 100 µl of media per well in tissue culture-treated black-walled, clear bottom Optilux 96-well plates (BD Biosciences) for 16-24 hours.

[001008] Prior to addition of compounds, cell media is removed and replaced with 75 µl of fresh media. Test compounds in DMSO are diluted 1:100 in media. The diluted test compounds are added to the cells (25 µl per well) in 3-fold dilutions with a final concentration range of 0.0015 to 10 µM. The cells are incubated for 30 minutes in a humidified chamber at 37°C with 5% CO_2. Immediately following compound incubation, all liquid is removed from the wells and cells are fixed with 4% paraformaldehyde in PBS (75 µl per well) for 15 minutes at room temperature. The paraformaldehyde solution is removed from wells and washed once with PBS (100 µl per well). The PBS is removed and cells are incubated with DRAQ5 Nucleur Dye (Alexis/Biostatus) (85 µl per well). The plates are covered with Flash Plate plastic adhesive foil and imaged on the Evotec Technologies OPERA Confocal Imager Opera after at least a 30 minute incubation. Concentration curves are generated by caluculating the Integrated Spot Intensity Per Cellular Signal decrease in test-compound treated samples relative to DMSO-treated controls and a 100% control inhibitor, and percentage inhibition values at a single concentration or growth inhibition (IC_{50}) values are determined from the curves. One skilled in the art will appreciate that the values generated either as percentage inhibition at a single concentration or IC_{50} values are subject to experimental variation.

[001009] As detailed above, compounds of the invention inhibit PI3K and/or VPS34. Examples of class I PI3-kinase isoforms are PI3K α, β, γ and δ. In certain embodiments, the compounds of the invention inhibit one or more isoforms of PI3K. In certain other embodiments, the compounds of the invention selectively inhibit one particular isoform of PI3K. For example, in some embodiments the compounds of the invention selectively inhibit PI3Kα. In some embodiments the compounds of the invention selectively inhibit PI3Kβ.

[001010] As used herein, selective inhibitor refers to compounds that inhibit one or more of the particular PI3K isoforms with at least about >10-fold, or at least about >20-fold, or at least about >30-fold selectivity for the one or more particular PI3K isoforms relative to other class I PI3-kinase isoforms in a biochemical assay. By way of example, compounds that inhibit PI3Kβ with at least about >10-fold, or at least about >20-fold, or at least about >30-fold selectivity relative to PI3K α, γ or δ are selective inhibitors

of PI3Kβ. Alternatively, compounds that inhibit PI3K β and δ with at least about >10-fold, or at least about >20-fold, or at least about >30-fold selectivity relative to PI3K α or γ are selective inhibitors of PI3K β and δ.

[001011] As detailed above, compounds of the invention inhibit PI3K. In certain embodiments, compounds inhibit one or more isoforms of PI3K. In other embodiments, compounds of the invention inhibit PI3Kalpha and have an $IC_{50} > 1.0$ μM. For example, these compounds include 2, 3, 5, 6, 7, 8, 9, 11, 12, 15, 16, 17, 18, 19, 21, 22, 23, 25, 26, 27, 33, 34, 36, 37, 39, 43, 44, 45, 46, 47, 49, 51, 52, 55, 58, 59, 60, 62, 63, 65, 66, 68, 69, 70, 73, 75, 76, 77, 78, 79, 80, 81, 84, 85, 87, 88, 89, 91, 92. In other embodiments, compounds of the invention have an $IC_{50} < 1.0$ μM but > 0.1 μM. For example, these compounds include compounds 1, 4, 10, 14, 20, 24, 28, 30, 31, 32, 35, 38, 40, 42, 48, 53, 54, 56, 57, 61, 64, 67, 71, 72, 74, 82, 83, 86, 90. In still other embodiments, compounds of the invention have an $IC_{50} <$ 0.1 μM. For example, these compounds include compounds 13, 29, 41, 50. In still other embodiments, compounds of the invention inhibit PI3Kbeta and have an $IC_{50} > 1.0$ μM. For example, these compounds include 2, 18, 22, 24, 29, 49, 55, 63, 67, 78. In other embodiments, compounds of the invention have an $IC_{50} < 1.0$ μM but > 0.1 μM. For example, these compounds include compounds 1, 4, 6, 8, 10, 12, 15, 17, 23, 25, 26, 27, 28, 32, 33, 34, 35, 37, 38, 39, 40, 42, 46, 47, 48, 53, 54, 56, 57, 58, 60, 61, 62, 64, 68, 69, 70, 71, 72, 73, 74, 76, 79, 82, 83, 84, 89. In still other embodiments, compounds of the invention have an $IC_{50} < 0.1$ μM. For example, these compounds include compounds 3, 5, 7, 9, 11, 13, 14, 16, 19, 20, 21, 30, 31, 36, 41, 43, 44, 45, 50, 51, 52, 59, 65, 66, 75, 77, 80, 81, 85, 86, 87, 88, 90, 91, 92.

[001012] In some embodiments, compounds of the invention inhibit PI3K α and β at a 1.1 μM concentration with the percent inhibition as shown in the table below.

Compound	PI3Kα Percent Inhibition	PI3Kβ Percent Inhibition	Compound	PI3Kα Percent Inhibition	PI3Kβ Percent Inhibition
91	27	105	**111**	7	77
93	9	80	**112**	95	110
94	58	97	**113**	25	100
95	68	101	**114**	40	106
96	58	109	**115**	45	97
97	53	101	**116**	46	98
98	58	111	**117**	48	94

99	12	72	**118**	28	104
100	20	98	**119**	9	88
101	30	105	**120**	18	97
102	30	78	**121**	11	59
103	2	71	**122**	49	106
104	26	109	**123**	64	105
105	21	98	**124**	79	109
106	58	103	**125**	46	99
107	49	103	**126**	42	103
108	44	100	**127**	40	110
109	6	76	**128**	46	106
110	5	41			

[001013] In some embodiments, compounds of the invention inhibit PI3K δ and γ at a 1.0 μM concentration with the percent inhibition as shown in the table below.

Compound	PI3Kδ Percent Inhibition	PI3Kγ Percent Inhibition	Compound	PI3Kδ Percent Inhibition	PI3Kγ Percent Inhibition
91	84.8	15.4	**112**	114.5	69.0
93	46.0	9.5	**113**	78.8	32.5
94	102.4	52.6	**114**	112.8	56.9
95	86.1	23.9	**115**	63.0	12.0
96	96.0	36.2	**116**	83.0	36.7
97	89.8	17.8	**117**	78.5	14.7
98	108.5	67.6	**118**	89.3	27.5
99	55.4	6.4	**119**	62.6	7.6
100	65.5	13.2	**120**	77.0	11.0
102	38.1	6.8	**121**	77.3	7.3
103	38.6	6.4	**122**	96.2	49.6
104	93.0	28.8	**123**	96.8	36.6
105	51.2	9.8	**124**	112.0	74.2
106	88.8	51.8	**125**	85.1	25.9
107	87.3	20.2	**126**	100.4	37.6
108	99.6	38.1	**127**	100.4	55.0
109	35.4	3.9	**128**	114.2	63.4
111	60.5	6.9			

[001014] In some embodiments, compounds of the invention inhibit VPS34 at a 1.0 μM concentration with the percent inhibition as shown in the tables below.

Compound	VPS34 Percent Inhibition	Compound	VPS34 Percent Inhibition	Compound	VPS34 Percent Inhibition
93	19.2	**106**	34.4	**119**	19.5
94	30.6	**107**	45.8	**120**	38.3
95	167.0	**108**	62.4	**121**	64.8
96	47.8	**109**	24.0	**122**	55.2
97	45.0	**111**	46.8	**123**	45.1
98	68.9	**112**	37.8	**124**	78.8
99	46.7	**113**	18.1	**125**	37.1
100	36.6	**114**	131.4	**126**	44.0
102	28.2	**115**	39.7	**127**	33.7
103	7.2	**116**	54.2	**128**	88.1
104	63.2	**117**	28.6		
105	22.6	**118**	68.2		

Compound	p110 alpha Percent Inhibition	p110 beta Percent Inhibition	p110 gamma Percent Inhibition	p110 delta Percent Inhibition
129	83	106	32	109
130	21	73	22	62
131	75	78	5	80
132	45	103	53	77
133	84	101	26	74
134	21	72	8	44
135	78	87	8	99
136	80	110	67	109
137	12	54	12	30

138	43	86	13	69
139	77	100	24	105
140	76	47	62	74
141	17	89	15	66
142	15	67	7	47
143	58	115	62	85
144	63	94	19	111
145	64	98	9	97
146	67	103	23	110
147	83	96	18	107
148	41	98	34	69
149	54	109	75	117
150	2	54	6	35
151	72	105	17	108
152	61	97	16	106
153	75	84	11	87
154	79	108	39	108
155	29	64	28	53
156	13	47	2	33
157	55	68	7	101
158	18	94	20	69
159	18	61	5	31
160	74	101	20	107
161	14	60	7	40
162	38	93	33	83
163	97	110	25	106
164	100	107	44	112
165	64	77	14	87
166	92	82	3	85
167	105	103	26	110
168	23	107	58	110
169	65	89	7	65
170	84	106	26	105

171	59	106	60	99
172	28	101	6	60
173	69	67	3	83
174	15	70	8	59
175	19	85	7	36
176	76	109	35	109
177	79	100	34	106
178	20	109	38	88
179	29	60	5	89
180	60	102	21	102
181	85	91	35	108
182	83	100	45	107
183	-2	16	3	9
184	76	112	16	112
185	16	97	9	50
186	68	109	65	92
187	32	95	25	77
188	47	94	36	82
189	89	96	21	106
190	3	60	7	33
191	26	97	30	90
192	48	90	12	100
193	26	69	13	46
194	17	18		
195	52	74	8	88
196	69	91	12	105
197	15	23	4	19
198	18	108	35	70
199	21	64	16	42
200	101	118	60	111
201	74	105	37	110
202	12	80	8	54
203	10	88	16	67

204	70	101	25	90
205	42	114	64	83
206	90	96	11	106
207	27	83	9	51
208	42	108	47	107
209	92	107	34	108
210	52	110	68	92
211	111	111	13	106
212	87	109	38	112
213	57	80	35	109
214	46	84	14	46
215	29	85	8	51
216	64	91	11	99
217	30	74	24	60
218	61	102	14	97
219	32	101	31	107
220	92	91	9	99
221	62	94	8	100
222	68	98	9	102
223	67	94	21	102
224	70	92	15	103
225	51	52	51	84
226	46	98	14	93
227	-2	76	3	24
228	24	94	11	57
229	62	105	16	106
230	57	93	29	102
231	34	104	47	77
232	38	105	26	67
233	61	97	28	74
234	60	100	10	104
235	65	101	17	66
236	11	53	10	48

237	61	89		
238	72	88	11	96
239	30	68	27	41
240	52	79	8	98
241	59	107	27	104
242	81	104	36	112
243	12	66	4	45
244	77	101	14	101
245	73	109	15	104
246	15	81	8	43
247	83	105	21	104
248	89	106	35	109
249	51	98	9	56
250	53	92	5	88
251	14	96	12	44
252	58	85	12	60
253	20	64	2	27
254	49	96	8	91
255	0	55	5	39
256	25	87	8	57
257	31	97	30	68
258	18	86	13	47
259	69	100	25	101
260	37	74	6	37
261	79	113	33	105
262	0	69	4	12
263	48	105	43	84
264	32	99	28	100
265	64	109	64	111
266	36	90	8	52
267	100	113	43	111
268	82	95	16	102
269	72	100	15	101

270	81	114	24	111
271	35	82	8	63
272	70	96	10	70
273	88	73	7	98
274	98	109	38	107
275	17	47	14	44
276	4	15	6	12
277	95	97	55	116
278	23	98	35	83
279	19	106	42	78
280	35	106	34	92
281	52	96	56	97
282	14	99	21	64
283	96	98	18	99
284	39	114	66	110
285	16	83	18	77
286	36	92	50	104
287	84	109	69	112
288	14	85	19	76
289	11	32	10	32
290	23	104	49	104
291	36	107	57	105
292	4	82	6	56
293	98	108	78	110
294	47	94	35	101
295	101	111	76	112
296	37	79	14	107
297	26	104	33	77
298	11	95	38	103
299	39	109	42	108
300	44	105	46	97
301	55	107	49	89
302	21	100	15	97

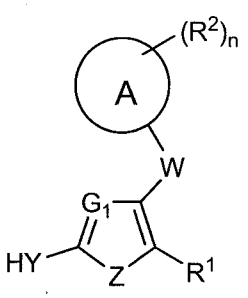
303	99	110	69	115
304	6	25	7	32
305	37	106	37	74
306	81	109	51	108
307	15	84	9	62
308	41	106	39	92
309	56	101	66	108
310	34	106	64	105
311	55	104	64	105
312	64	105	47	92
313	73	117	30	86
314	42	109	42	104
315	97	110	75	114
316	78	106	62	111
317	20	77	29	70
318	18	96	14	76
319	59	105	50	113
320	16	94	35	97
321	67	73	59	86
322	64	104	28	67
323	66	61	46	97
324	107	118	67	113
325	17	89	22	89
326	79	108	56	96
327	34	109	22	109
328	11	98	48	83
329	39	112	29	80
330	85	109	61	106
331	37	105	51	107
332	11	77	27	91
333	63	95	55	74
334	21	103	12	101
335	54	111	31	107

336	16	90	10	49
337	14	60	11	46
338	67	110	73	109
339	20	86	12	55
340	48	113	59	104
341	30	110	30	98
342	34	80	12	97
343	84	110	67	113
344	24	103	59	102
345	64	105	62	83
346	21	98	23	98
347	71	102	60	111
348	4	63	4	56
349	43	108	42	96
350	6	58	3	41
351	15	82	46	79
352	18	85	14	84
353	19	87	15	80
354	89	111	40	99
355	44	100	53	105
356	11	95	23	72
357	89	110	79	110
358	13	43	32	51
359	90	109	64	102
360	30	106	49	110
361	104	115	60	111
362	80	116	44	104
363	99	113	65	106
364	88	109	56	101
365	105	117	63	112
366	66	113	77	113
367	99	110	72	116
368	89	112	87	113

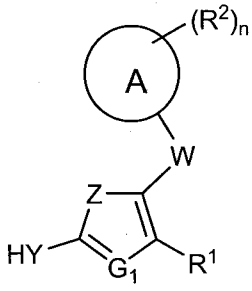
369	109	115	65	109
370	22	98	12	62

[001015] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments, which utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments, which have been represented by way of example.

1. A compound of formula **IA-a** or **IB-a**:



IA-a

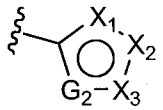


IB-a

or a pharmaceutically acceptable salt thereof, wherein:

Z is S or Se;

R^1 is CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N\text{-}NH_2)NH_2$, $-C(=N)N(R^3)_2$, wherein:

CY is  ; wherein:

G_2 is –N= , =N–, or $-N(R^{3'})-$, wherein:

each occurrence of R^3 and $R^{3'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_1, X_2, and X_3, are each independently N, $NR^{3'}$, O, S, or CR^4, provided that only one of X_1, X_2, or X_3 may be O, S, or $NR^{3'}$;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $-Z_3\text{-}R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$, $-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, or -OC(O)-;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic,

3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-

10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein two adjacent occurrences of $R^{3'}$ or R^4, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or $-CN$;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5

heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

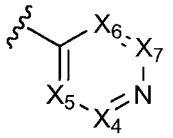
G_1 is N or $-CR^8$, wherein R^8 is H, –CN, halogen, $–Z_2-R^9$, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, or -OC(O)-;

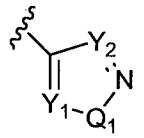
R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

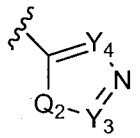
HY is an optionally substituted group selected from:



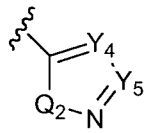
A ,



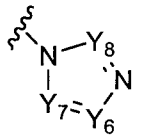
B ,



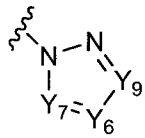
C ,



D



E ,



or **F** ;

wherein each occurrence of X_4, X_5, X_6, and X_7 is independently $–CR^{10}$ or N, provided no more than two occurrences of X_4, X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $–NR^5$;

each occurrence of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, and Y_9 is independently $-CR^{10}$ or N, provided no more than two occurrences of Y_6, Y_7, Y_8, and Y_9 are N;

or wherein two adjacent occurrences of X_4 and X_5, X_6 and X_7, Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein R^{10} is $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, or $-V_1-T_1-R^{10b}$ wherein:

V_1 is $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, or $-SO_2NR^{11}-$;

each occurrence of R^{10a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ or wherein T_1 forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

each occurrence of R^{10b} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{10c} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

R^{10a} and R^{10c} taken together with a nitrogen atom to which they are bound form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{11} is independently hydrogen, $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

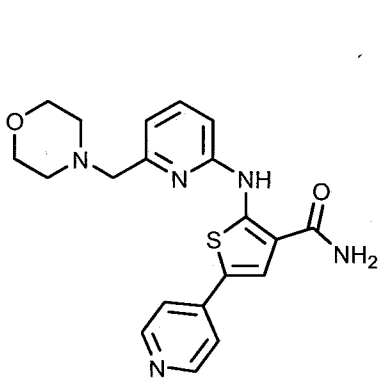
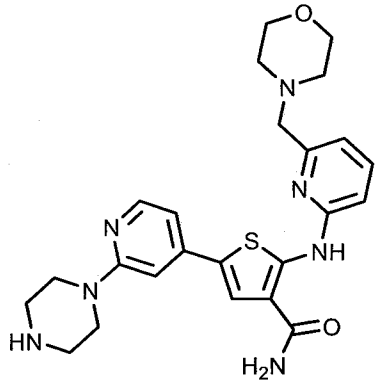
wherein each occurrence of R^{11a} is independently hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^5 is independently hydrogen, $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

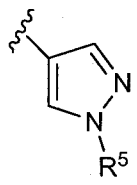
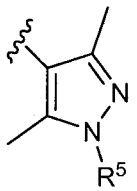
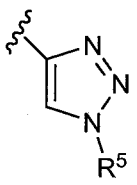
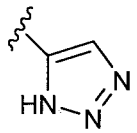
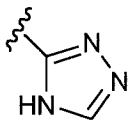
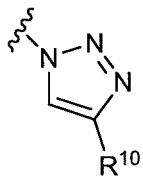
wherein each occurrence of R^{5a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{5b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R^{5b} taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, provided that:

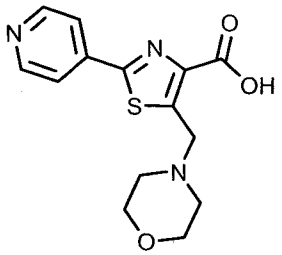
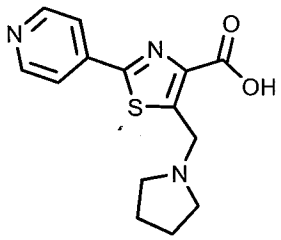
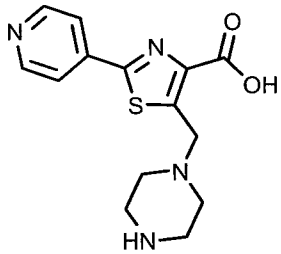
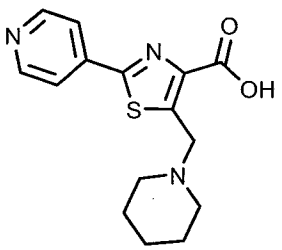
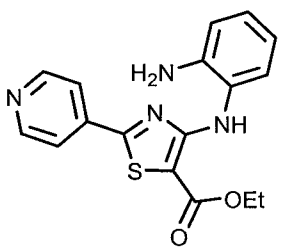
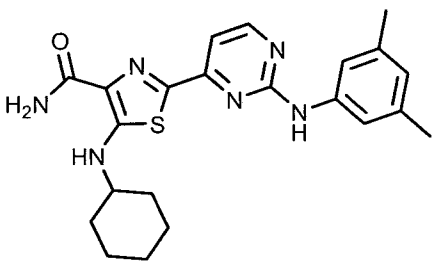
a) for compounds of formula IB-a compounds are other than:

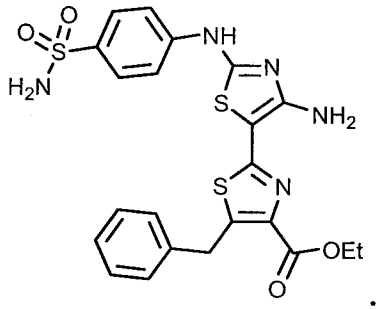

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; and

when G^1 is CR^8, R^1 is $CONH_2$, and W is NH, then HY is other than

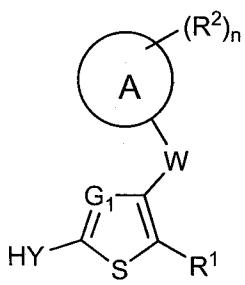

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, or ; and

b) the compound is other than:

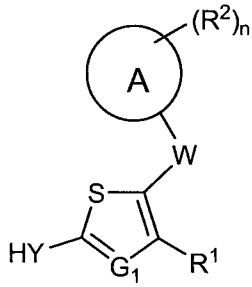

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2. A compound of formula **IA** or **IB**:



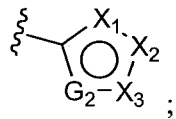
IA



IB

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N\text{-}NH_2)NH_2$, $-C(=N)N(R^3)_2$, wherein:

CY is  ; wherein:

G_2 is –N= , =N–, or $–N(R^{3'})$ –, wherein:

each occurrence of R^3 and $R^{3'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_1, X_2, and X_3, are each independently N, $NR^{3'}$, O, S, or CR^4, provided that only one of X_1, X_2, or X_3 may be O, S, or $NR^{3'}$;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $–Z_3\text{-}R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})$-, -S-, -S(O)-, $-S(O)_2$-, -C(O)-, $-CO_2$-, $-C(O)NR^{4a}$-, $-N(R^{4a})C(O)$-,

$-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$,
$-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, or $-OC(O)-$;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic,

3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein two adjacent occurrences of $R^{3'}$ or R^4, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered

aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or $-CN$;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from

a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

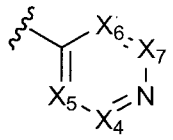
G_1 is N or $-CR^8$, wherein R^8 is H, –CN, halogen, $–Z_2–R^9$, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2$-, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, or -OC(O)-;

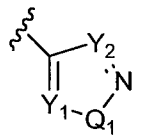
R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

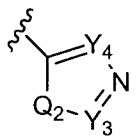
HY is an optionally substituted group selected from:



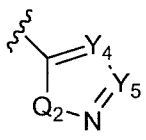
A ,



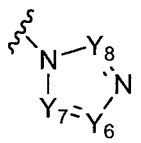
B ,



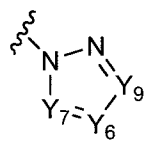
C ,



D



E ,



or **F** ;

wherein each occurrence of X_4, X_5, X_6, and X_7 is independently $–CR^{10}$ or N, provided no more than two occurrences of X_4, X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $–NR^5$;

each occurrence of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, and Y_9 is independently $-CR^{10}$ or N, provided no more than two occurrences of Y_6, Y_7, Y_8, and Y_9 are N;

or wherein two adjacent occurrences of X_4 and X_5, X_6 and X_7, Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein R^{10} is $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, or $-V_1-T_1-R^{10b}$ wherein:

V_1 is $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, or $-SO_2NR^{11}-$;

each occurrence of R^{10a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T_1 is an optionally substituted C_1.C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ or wherein T_1 forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

each occurrence of R^{10b} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{10c} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-

10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

R^{10a} and R^{10c} taken together with a nitrogen atom to which they are bound form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{11} is independently hydrogen, $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{11a} is independently hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^5 is independently hydrogen, $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

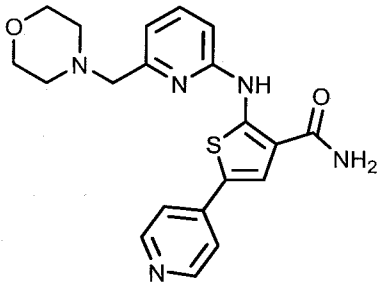
wherein each occurrence of R^{5a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{5b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R^{5b} taken together with the nitrogen atom to which they are bound, form an optionally

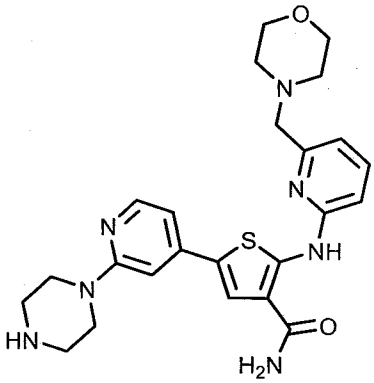
substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

a) for compounds of formula IB compounds are other than:

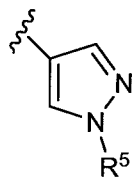


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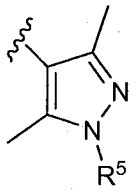


; and

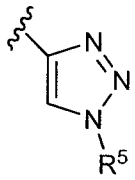
when G^1 is CR^8, R^1 is $CONH_2$, and W is NH, then HY is other than



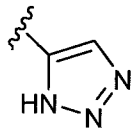
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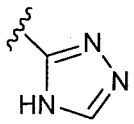
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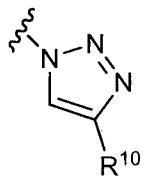
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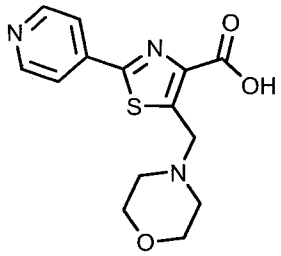
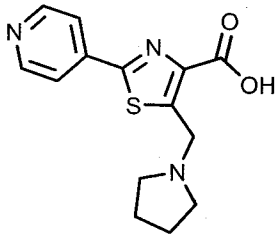
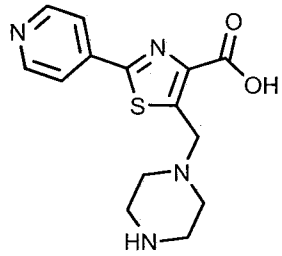
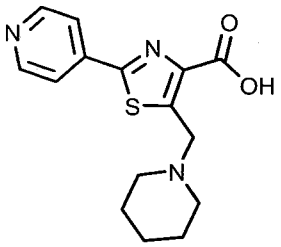
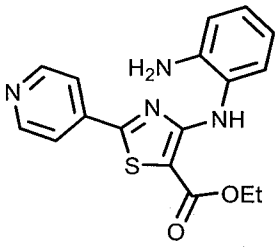
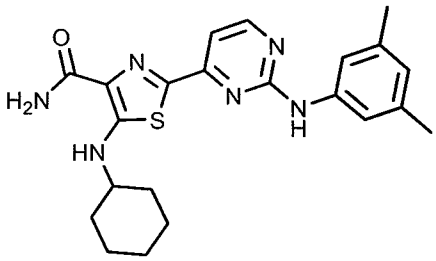
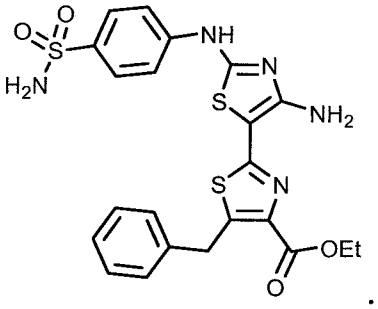


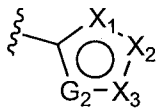
,



, or ; and

b) the compound is other than:

3. The compound of claim 1 or 2, wherein R^1 is CY, and CY is .

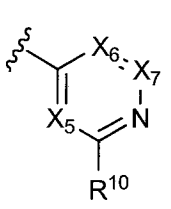
4. The compound of claim 1 or 2, wherein X_1 is N, G_2 is -N($R^{3'}$)-, and X_2 and X_3 are CH.

5. The compound of claim 1 or 2,wherein X_1 and X_2 are N, G_2 is -N($R^{3'}$)-, and X_3 is CH.

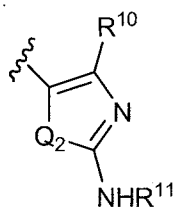
6. The compound of claim 1 or 2, wherein X_3 is N, G_2 is -N($R^{3'}$)-, and X_1 and X_2 are CH.

7. The compound of claim 1 or 2, wherein X_1 is N, X_2 is CH, X_3 is –N($R^{3'}$)- and G_2 is =N-.

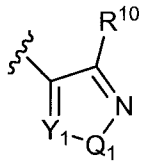
8. The compound of claim 1 or 2, wherein HY is selected from:



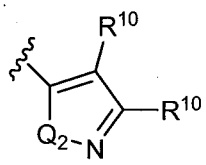
H ,



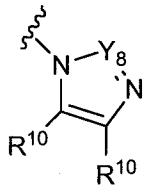
J ,



K ,



L , or



M;

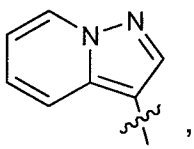
wherein each occurrence of X_5, X_6, and X_7 is independently $-CR^{10}$ or N, provided no more than two occurrences of X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $-NR^5$;

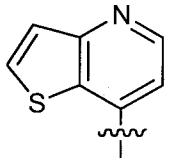
each occurrence of Y_1 and Y_7 is independently $-CR^{10}$ or N;

or wherein two adjacent occurrences of X_6 and X_7, or Y_1 and Q_1, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

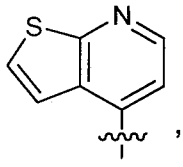
9. The compound of claim 8, wherein HY is selected from:



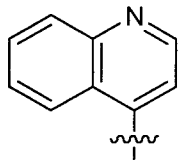
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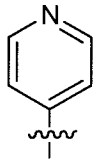
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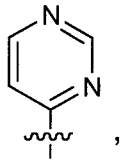
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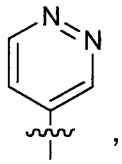
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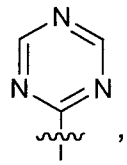
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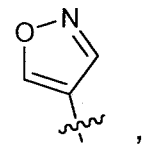
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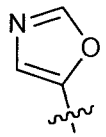
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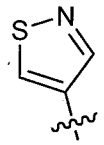
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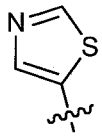
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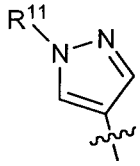
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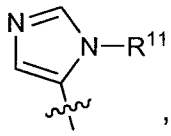
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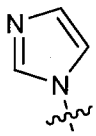
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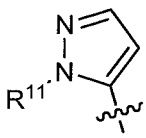
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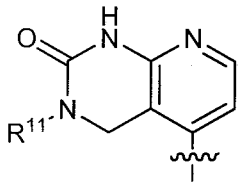
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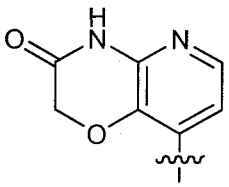
xv



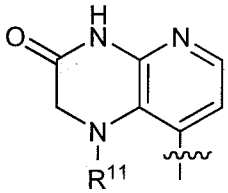
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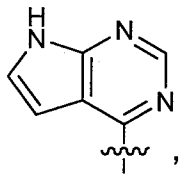
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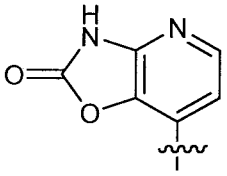
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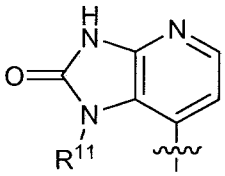
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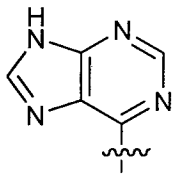
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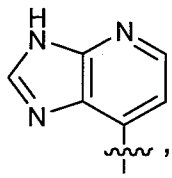
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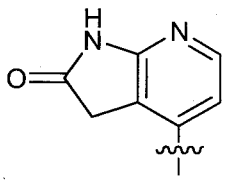
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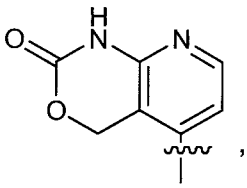
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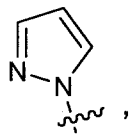
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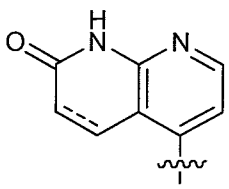
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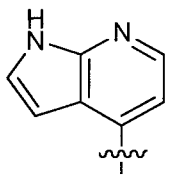
xxvi



xxvii



, or

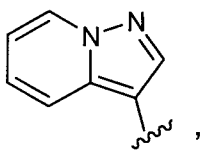
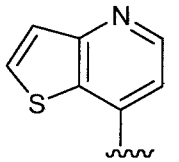
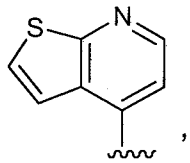
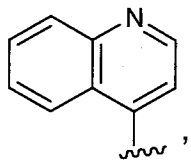


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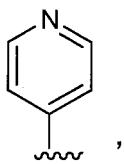
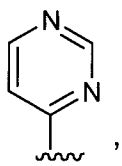
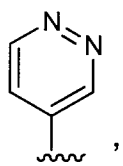
xxviii **xxix**

wherein each HY group is optionally additionally substituted with one or more occurrences of R^{10}, and ====== in **xviii** represents a single bond or a double bond.

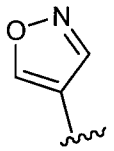
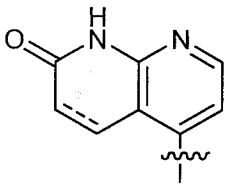
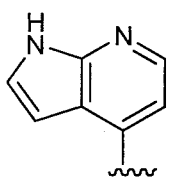
10. The compound of claim 9, wherein HY is selected from:

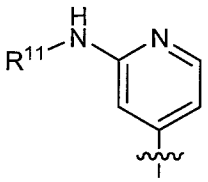
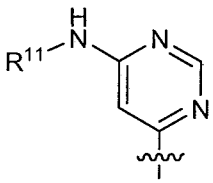
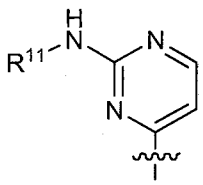
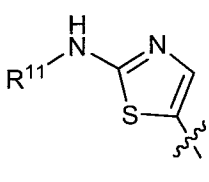
i **ii** **iii** **iv**

v **vi** **vii**

ix **xxviii** **xxix**

xxx **xxxi** **xxxii** **xxxiii**

wherein each HY group is optionally additionally substituted with one or more occurrences of R^{10}, and ====== in **xviii** represents a single bond or a double bond.

11. The compound of claim 1 or 2, wherein G_1 is $C(R^8)$.

12. The compound of claim 1 or 2, wherein G_1 is CH.

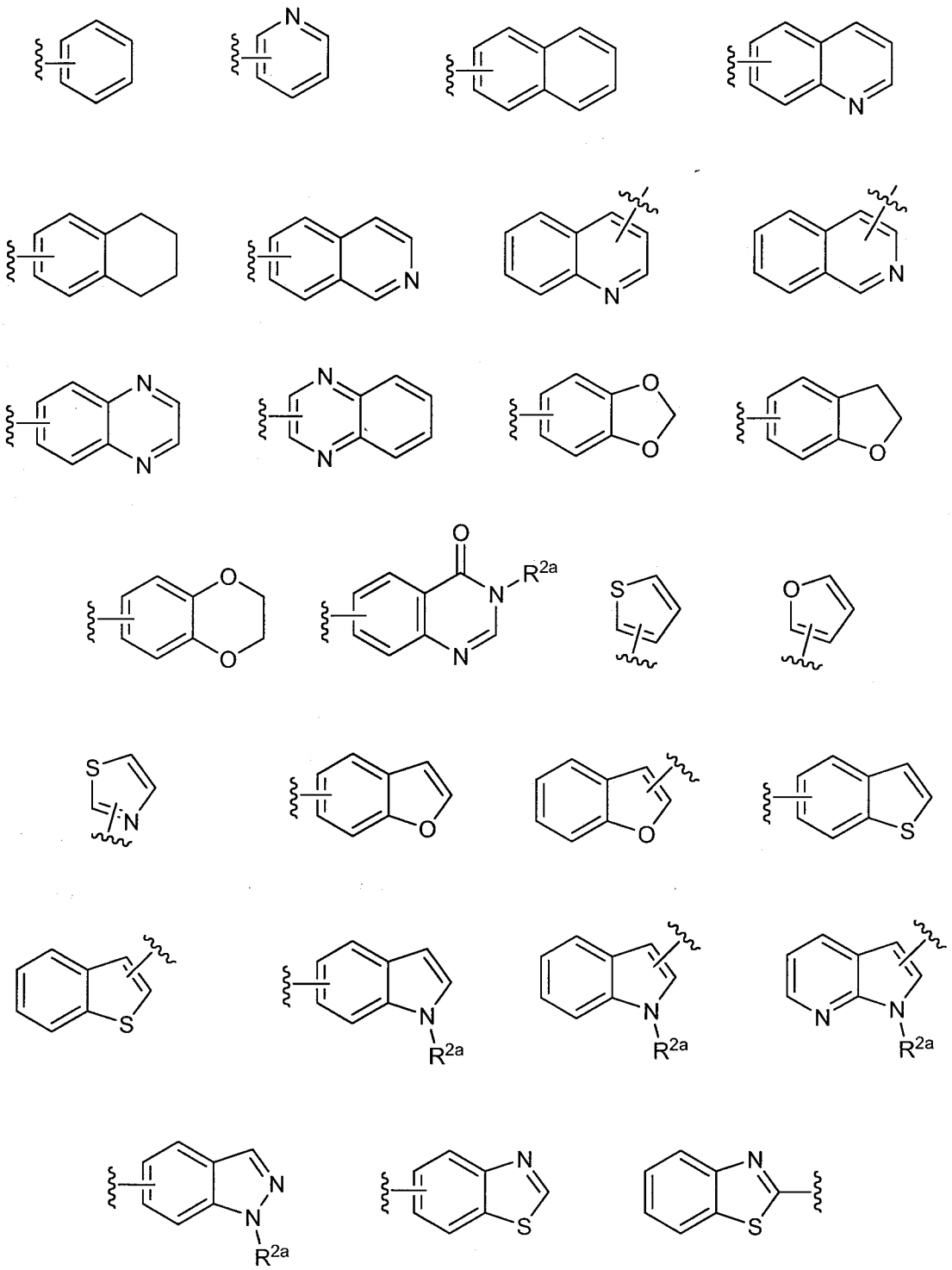
13. The compound of claim 1 or 2, wherein G_1 is N.

14. The compound of claim 1 or 2, wherein W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or –CN; and wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring.

15. The compound of claim 14, wherein W is $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, or $-N(R^{7a})C(O)-$, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

16. The compound of claim 1 or 2, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

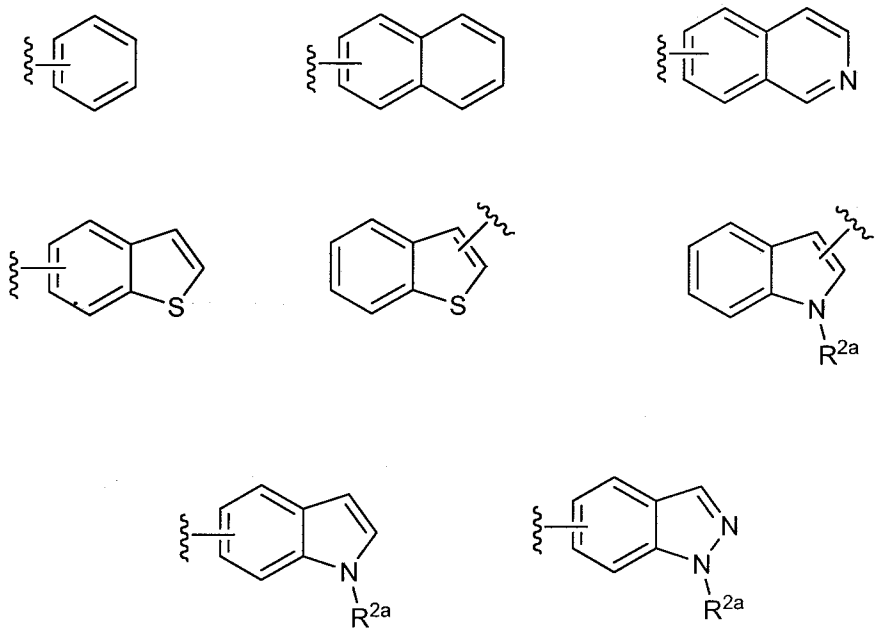
17. The compound of claim 16, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

18. The compound of claim 16, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

19. The compound of claim 16, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

20. The compound of claim 16, wherein:

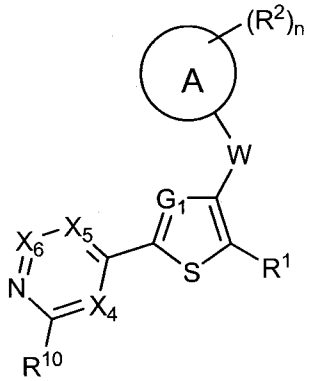
ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

21. The compound of claim 19, wherein ring A is a naphthyl group, R^2 is halogen and n is 1 to 2.

22. The compound of claim 19, wherein ring A is a naphthyl group and n is 0.

23. The compound of claim 20, wherein Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

24. A compound having the following formula **II**:



II

wherein:

X_4, X_5 and X_6 are each independently $-CR^{10}$ or N, provided no more than two occurrences of X_4, X_5 and X_6 are N;

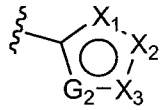
or two adjacent groups selected from R^{10}, X_4, X_5, and X_6, taken together, form an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

25. The compound of claim 24, wherein one of X^4, X^5, or X^6 is N.

26. The compound of claim 24, wherein all of X^4, X^5, or X^6 are CR^{10}.

27. The compound of claim 24, wherein each occurrence of R^{10} is independently selected from –CN, $-OR^{10a}$, $-N(R^{11})_2$, halogen, C_{1-4}alkyl, $-N(R^{11})COR^{10a}$, or wherein two occurrences of

R^{10}, taken together with the atoms to which they are bound form an optionally substituted group selected from a fused 5- or 6-membered cycloaliphatic, 4-10-membered heterocyclyl, 6-10-membered aryl or 5-10-membered heteroaryl ring, wherein the heterocyclyl and heteroaryl rings have 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

28. The compound of claim 24, wherein R^1 is CY, and CY is .

29. The compound of claim 28, wherein X_1 is N, G_2 is -N($R^{3'}$)-, and X_2 and X_3 are CH.

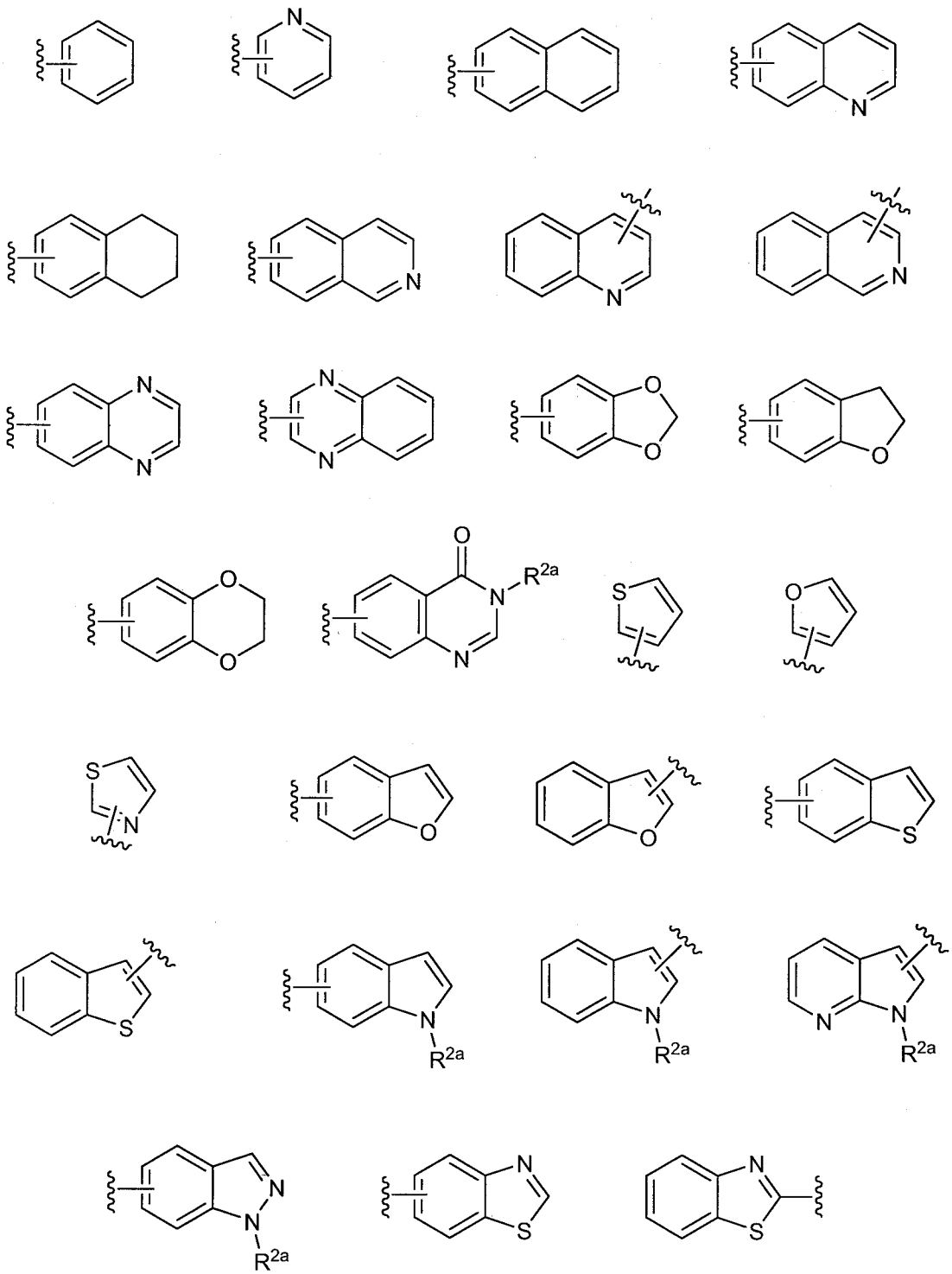
30. The compound of claim 28, wherein X_1 and X_2 are N, G_2 is -N($R^{3'}$)-, and X_3 is CH.

31. The compound of claim 28, wherein X_3 is N, G_2 is -N($R^{3'}$)-, and X_1 and X_2 are CH.

32. The compound of claim 28, wherein X_1 is N, X_2 is CH, X_3 is –N($R^{3'}$)- and G_2 is =N-.

33. The compound of claim 24, wherein Ring A is an optionally substituted 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

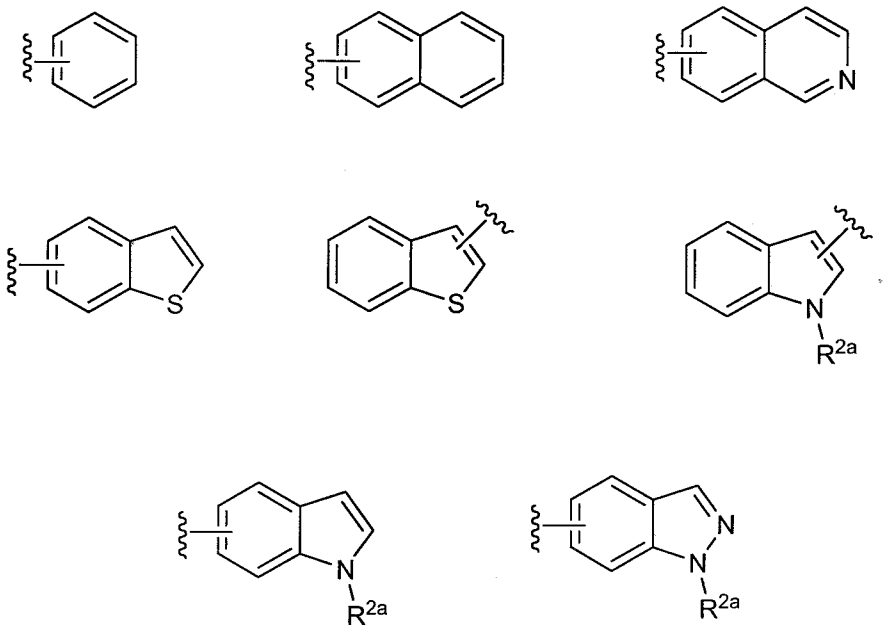
34. The compound of claim 33, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

35. The compound of claim 33, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

36. The compound of claim 33, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

37. The compound of claim 33, wherein Ring A is a phenyl group optionally substituted with 1-3 independent occurrences of halogen, C_{1-3} alkyl, -CN, C_{1-3}haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, $NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

38. The compound of claim 36, wherein ring A is a naphthyl group, R^2 is halogen and n is 1 to 2.

39. The compound of claim 38, wherein ring A is a naphthyl group and n is 0.

40. The compound of claim 37, wherein Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

41. The compound of claim 24, wherein W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is selected from hydrogen, optionally substituted C_{1-4} aliphatic, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or –CN; and

wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic;

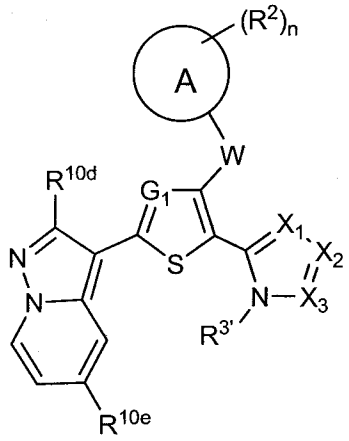
each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

42. The compound of claim 41, wherein W is $-C(H)(N(R^{7b})_2)-$,, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, or $-N(R^{7a})C(O)-$, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

43. A compound having the formula **III**:



III

wherein R^{10d} is hydrogen or optionally substituted C_{1-4}alkyl, and R^{10e} is R^{10}.

44. The compound of claim 43, wherein R^{10e} is $-T_1-R^{10b}$, or hydrogen.

45. The compound of claim 43, wherein R^{10e} is hydrogen, $-CH_2N(R^{11})_2$, or $-CH_2N(R^{11})C(=NR^{11})N(R^{11})_2$, wherein R^{11} is $-C(O)R^{11a}$, an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

46. The compound of claim 45, wherein when R^{11} is an optionally substituted C_{1-6} aliphatic group, the C_{1-6} aliphatic group is further defined as $-(CH_2)_xR^{11b}$ or $-(CH_2)_xN(R^{11b})_2$, $-(CH_2)_xN(R^{11b})C(O)R^{11b}$, or $-(CH_2)_xN(R^{11b})C(O)OR^{11b}$, wherein R^{11b} is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and x is 1 to 3.

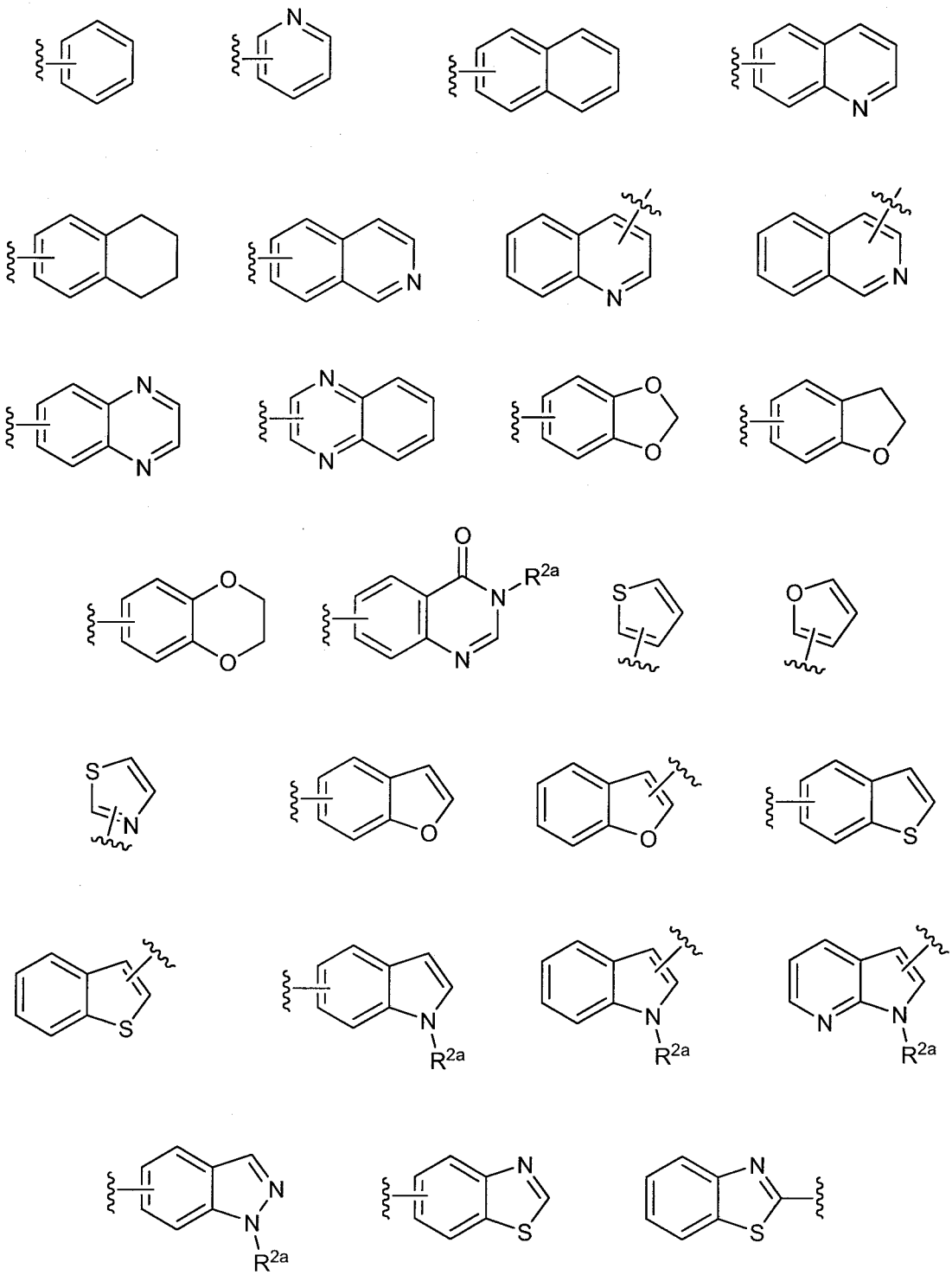
47. The compound of claim 43, wherein X_1 is N, and X_2 and X_3 are CH.

48. The compound of claim 43, wherein X_1 and X_2 are N, and X_3 is CH.

49. The compound of claim 43, wherein X_3 is N, and X_1 and X_2 are CH.

50. The compound of claim 43, wherein Ring A is an optionally substituted 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

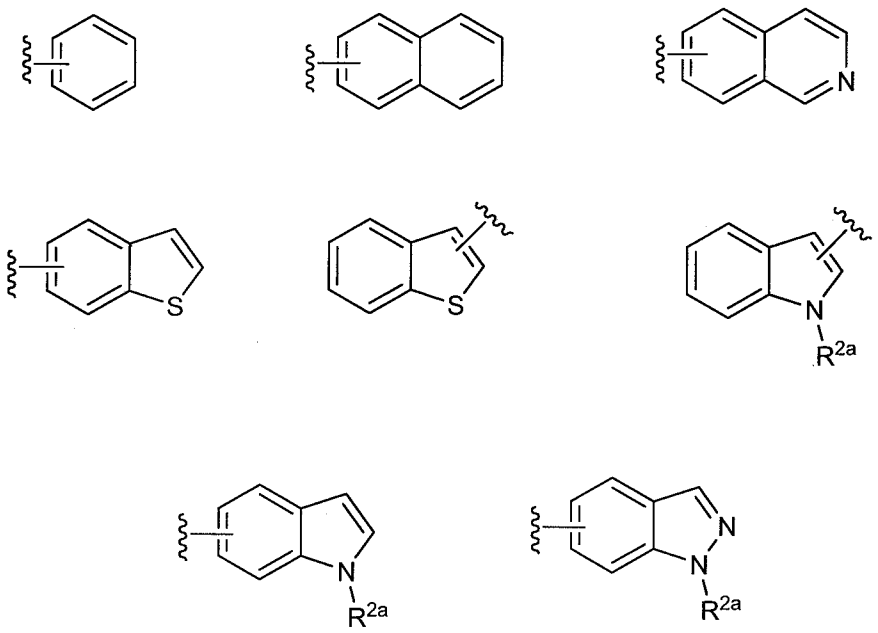
51. The compound of claim 50, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

52. The compound of claim 50, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

53. The compound of claim 50, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

54. The compound of claim 50, wherein Ring A is a phenyl group optionally substituted with 1-3 independent occurrences of halogen, C_{1-3} alkyl, -CN, C_{1-3}haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

55. The compound of claim 54, wherein Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

56. The compound of claim 53, wherein ring A is a naphthyl group, R^2 is halogen and n is 1 to 2.

57. The compound of claim 56, wherein ring A is a naphthyl group and n is 0.

58. The compound of claim 43, wherein W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is selected from hydrogen, optionally substituted C_{1-4} aliphatic, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or -CN; and

wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic;

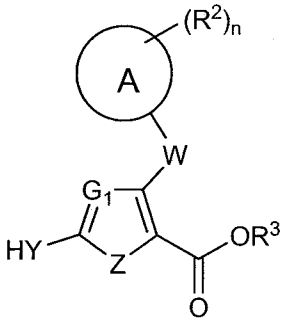
each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

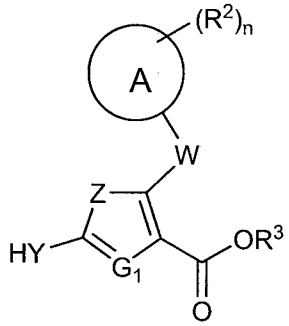
any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

59. The compound of claim 58, wherein W is $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, or $-N(R^{7a})C(O)-$, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

60. A compound of formula **IA-i-a** or **IB-i-a**:



IA-i-a



IB-i-a

or a pharmaceutically acceptable salt thereof, wherein:

Z is S or Se;

R^3 is hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, or:

two adjacent R^2 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having

1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen, $-N(R^{7b})_2$, or an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

W is selected from a covalent bond, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7c}$, $-SR^{7a}$, or F;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

each occurrence of R^{7c} is independently an optionally substituted C_{1-6}aliphatic or an optionally substituted 3-7 membered cycloalphatic; or

wherein any two occurrences of R^7, R^{7a}, R^{7b} , or R^{7c}, taken together with atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

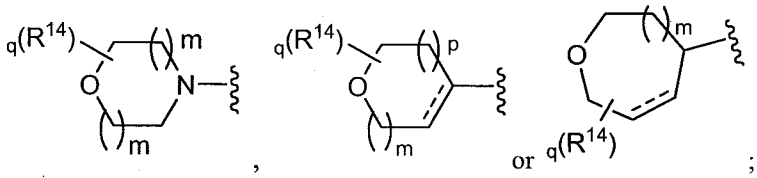
or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N or $-CR^8$, wherein R^8 is H, –CN, halogen, $–Z_2-R^9$, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, or -OC(O)-;

R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

HY is , , or ;

$\overline{\overline{\overline{\overline{\overline{\overline{}}}}}}$ represents a single bond or a double bond;

wherein each occurrence of R^{14} is independently–R^{14a} or $-T_1-R^{14d}$, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, $-NO_2$, $-R^{14c}$, $-N(R^{14b})_2$, $-OR^{14b}$, $-SR^{14c}$, $-S(O)_2R^{14c}$, $-C(O)R^{14b}$, $-C(O)OR^{14b}$, $-C(O)N(R^{14b})_2$, $-S(O)_2N(R^{14b})_2$, $-OC(O)N(R^{14b})_2$, $-N(R^{14e})C(O)R^{14b}$, $-N(R^{14e})SO_2R^{14c}$, $-N(R^{14e})C(O)OR^{14b}$, $-N(R^{14e})C(O)N(R^{14b})_2$, or

$-N(R^{14c})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

T_1 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, or $-C(O)N(R^{14a})-O-$ or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

n is 0-6;

q is 0-4;

m is 1 or 2; and

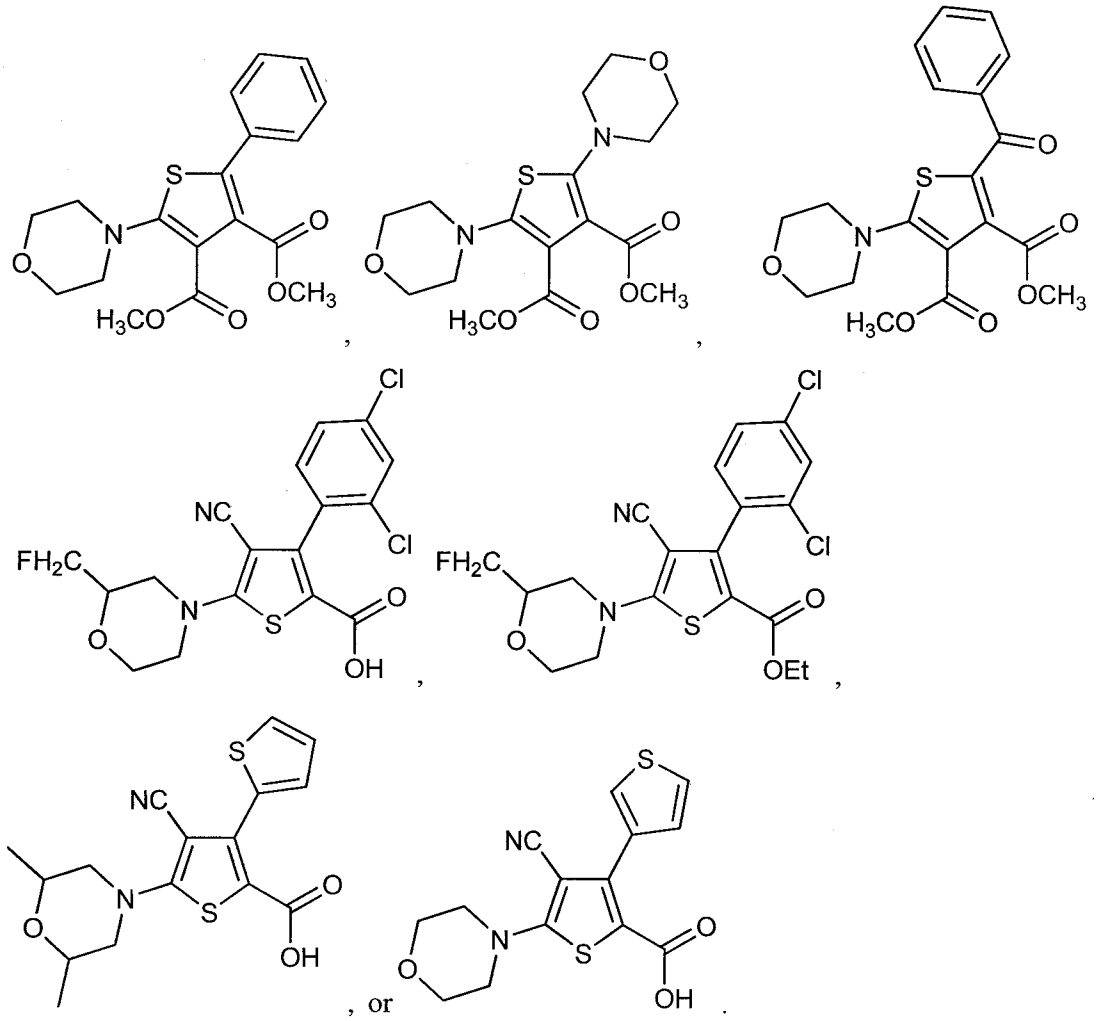
p is 0, 1, or 2;

provided that for compounds where Z is S:

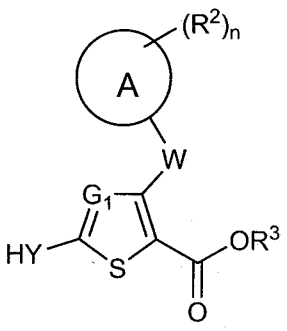
a) when G_1 is C-CN, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

b) when G_1 is N, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

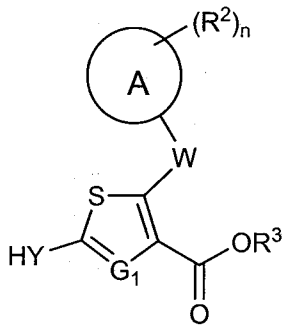
c) the compound is other than:



61. A compound of formula **IA** or **IB**:



IA-i



IB-i

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, or:

two adjacent R^2 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12a} is independently halogen, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered

aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen, $-N(R^{7b})_2$, or an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

W is selected from a covalent bond, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7c}$, $-SR^{7a}$, or F;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

each occurrence of R^{7c} is independently an optionally substituted C_{1-6}aliphatic or an optionally substituted 3-7 membered cycloalphatic; or

wherein any two occurrences of R^7, R^{7a}, R^{7b} , or R^{7c}, taken together with the atom to which they are bound, form an optionally substituted group selected

from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

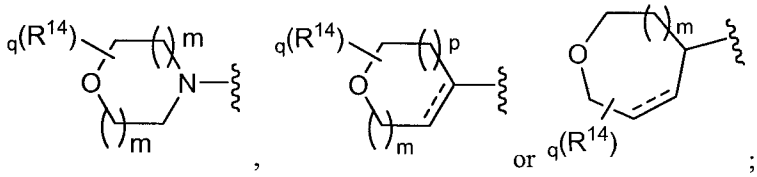
or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N or $-CR^8$, wherein R^8 is H, –CN, halogen, $–Z_2-R^9$, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, or -OC(O)-;

R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

HY is , , or ;

====== represents a single bond or a double bond;

wherein each occurrence of R^{14} is independently–R^{14a} or $-T_1-R^{14d}$, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, $-NO_2$, $-R^{14c}$, $-N(R^{14b})_2$, $-OR^{14b}$, $-SR^{14c}$, $-S(O)_2R^{14c}$, $-C(O)R^{14b}$, $-C(O)OR^{14b}$, $-C(O)N(R^{14b})_2$, $-S(O)_2N(R^{14b})_2$, $-OC(O)N(R^{14b})_2$, $-N(R^{14e})C(O)R^{14b}$, $-N(R^{14e})SO_2R^{14c}$, $-N(R^{14e})C(O)OR^{14b}$, $-N(R^{14e})C(O)N(R^{14b})_2$, or $–N(R^{14e})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered

heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

T_1 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, or $-C(O)N(R^{14a})-O-$ or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

n is 0-6;

q is 0-4;

m is 1 or 2; and

p is 0, 1, or 2;

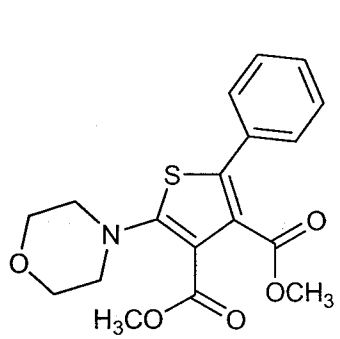
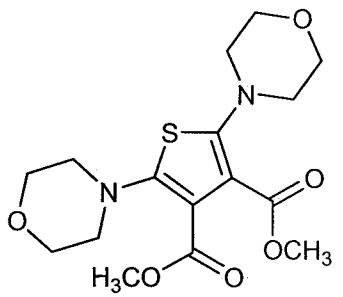
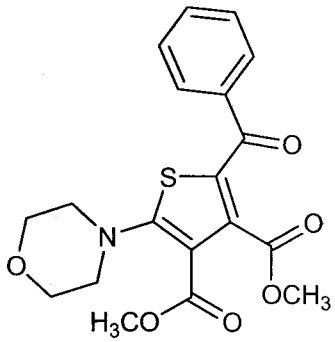
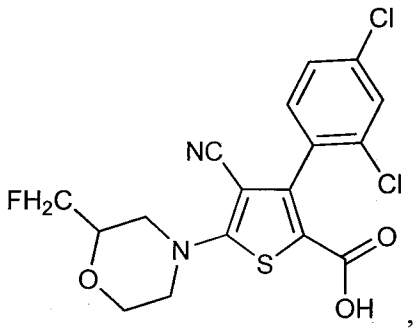
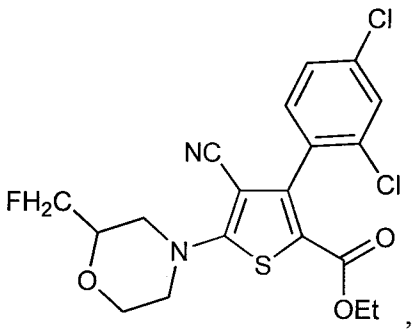
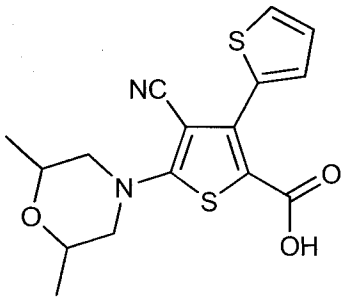
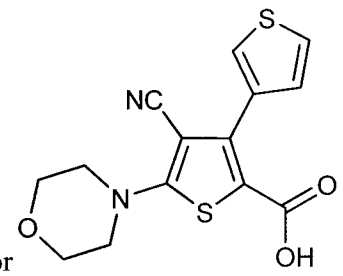
provided that:

a) when G_1 is C-CN, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl,

3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

b) when G_1 is N, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

c) the compound is other than:


,

,


,

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, or

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62. The compound of claim 60 or 61, wherein G_1 is N.

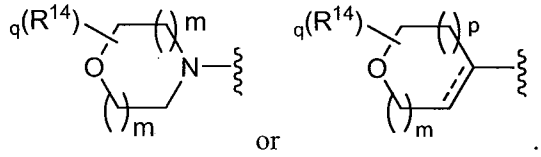
63. The compound of claim 60 or 61, wherein G_1 is $C(R^8)$.

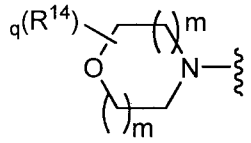
64. The compound of claim 63, wherein R^8 is –CN, halogen, or C_{1-6} aliphatic.

65. The compound of claim 63, wherein R^8 is C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl.

66. The compound of claim 63, wherein R^8 is –CN or C_{2-4} alkynyl.

67. The compound of claim 60 or 61, wherein HY is selected from:



68. The compound of claim 67, wherein HY is .

69. The compound of claim 88, wherein both occurrences of m are 1.

70. The compound of claim 88, wherein q is 0.

71. The compound of claim 60 or 61, wherein R^3 is H.

72. The compound of claim 60 or 61, wherein R^3 is C_{1-6} aliphatic.

73. The compound of claim 62, wherein R^3 is C_{1-4} alkyl.

74. The compound of claim 63, wherein R^3 is methyl or ethyl.

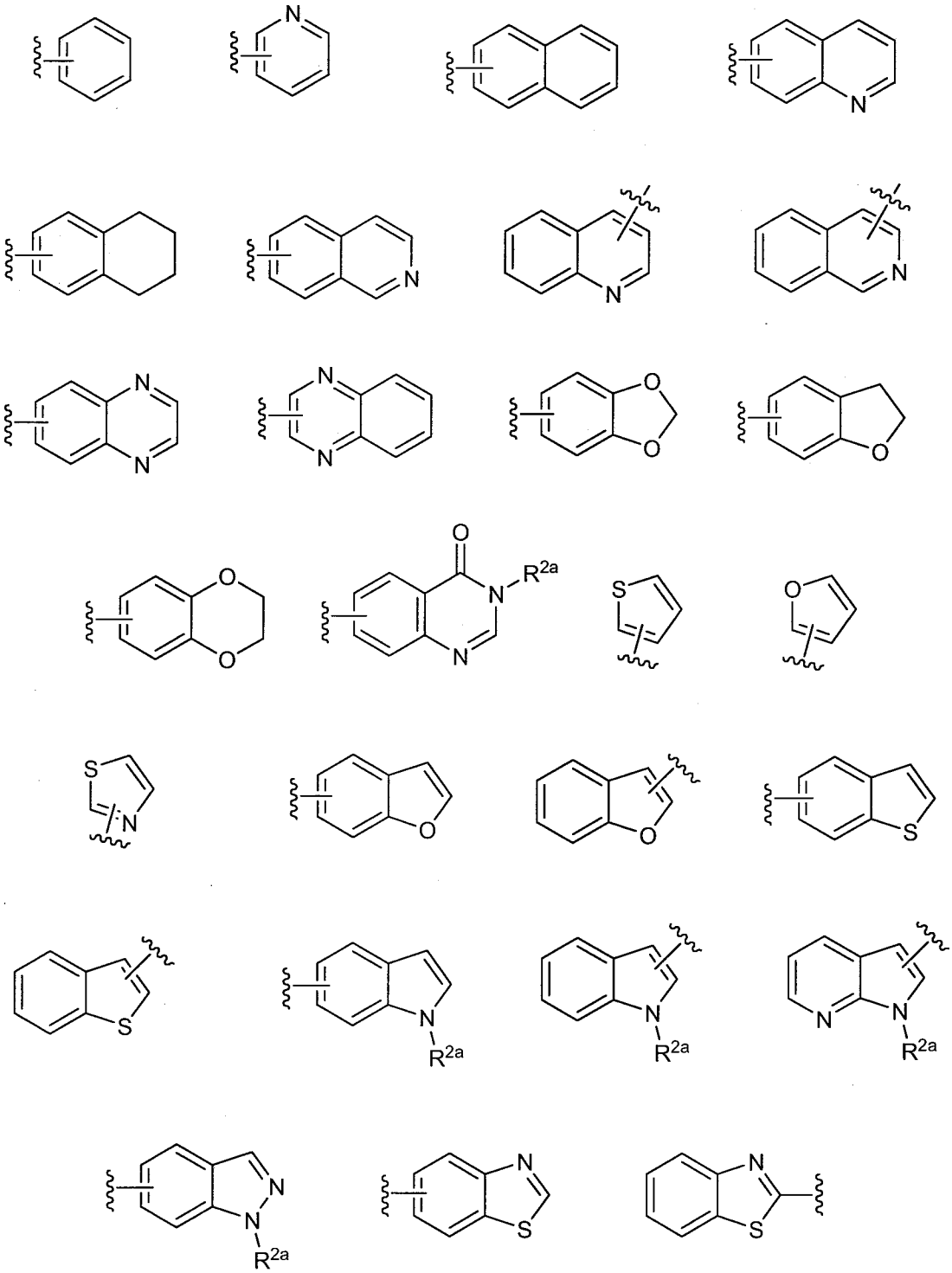
75. The compound of claim 60 or 61, wherein W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-N(R^{7b})_2$, or F; and wherein each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring; and each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

76. The compound of any one of claims 60 or 61, wherein W is $-C(H)(N(R^{7b})_2)-$ or $-CH_2-$, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

77. The compound of any one of claims 60 or 61, wherein W is a covalent bond.

78. The compound of claim 60 or 61, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

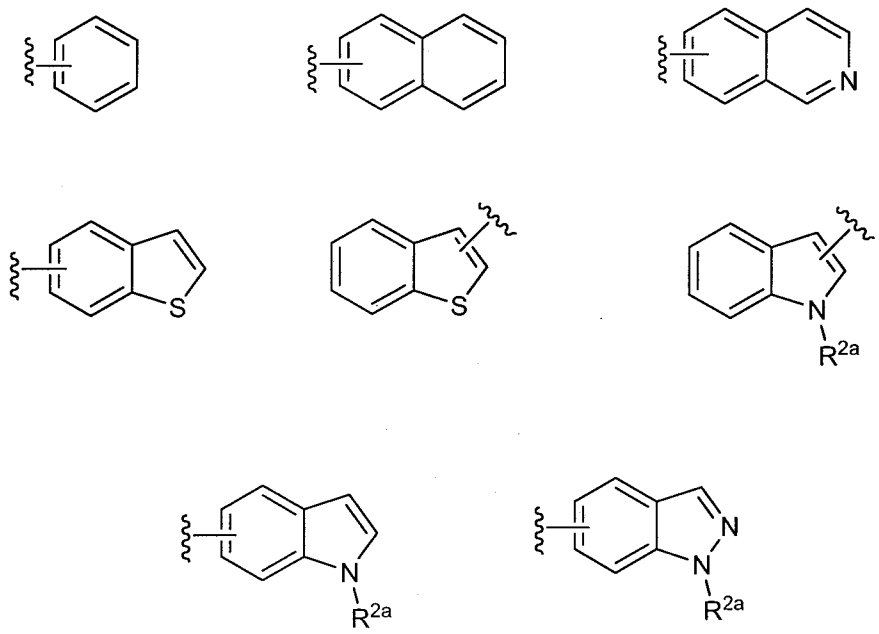
79. The compound of claim 60 or 61, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

80. The compound of claim 60 or 61wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

81. The compound of claim 80, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

82. The compound of claim 60 or 61, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is –C(H)($N(R^{7b})_2$)- or -CH_2-, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

83. The compound of claim 82, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-CH_2-$.

84. The compound of claim 60 or 61, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

85. The compound of claim 84, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OC_{1-3}$ alkyl, or $-OC_{1-3}$ haloalkyl; and n is 0 to 3.

86. The compound of claim 85, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OCH_3$, or $-OCF_3$; and n is 0 to 3.

87. The compound of claim 60 or 61, wherein Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

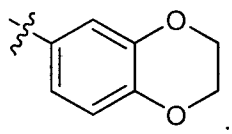
88. The compound of claim 60 or 61, wherein Ring A is a phenyl group, n is 1, and R^2 is in the para position.

89. The compound of claim 60 or 61, wherein Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions.

90. The compound of claim 60 or 61, wherein ring A is a naphthyl group, R^2 is halogen and n is 0, 1 or 2.

91. The compound of claim 60 or 61, wherein ring A is a naphthyl group and n is 0.

92. The compound of claim 90, wherein Ring A is a 2-naphthyl group.

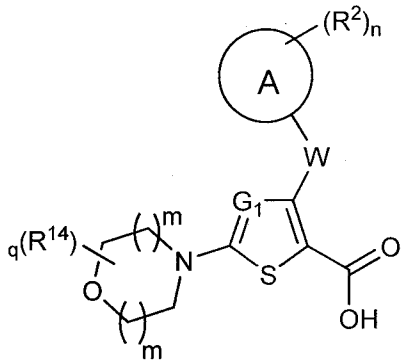
93. The compound of claim 60 or 61, wherein Ring A is .

94. The compound of claim 60 or 61, wherein Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

95. The compound of claim 94, wherein Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring.

96. The compound of claim 95, wherein Ring A is substituted with one or more C_{1-3} alkyl groups.

97. A compound having the following formula **II-A**:



II-A.

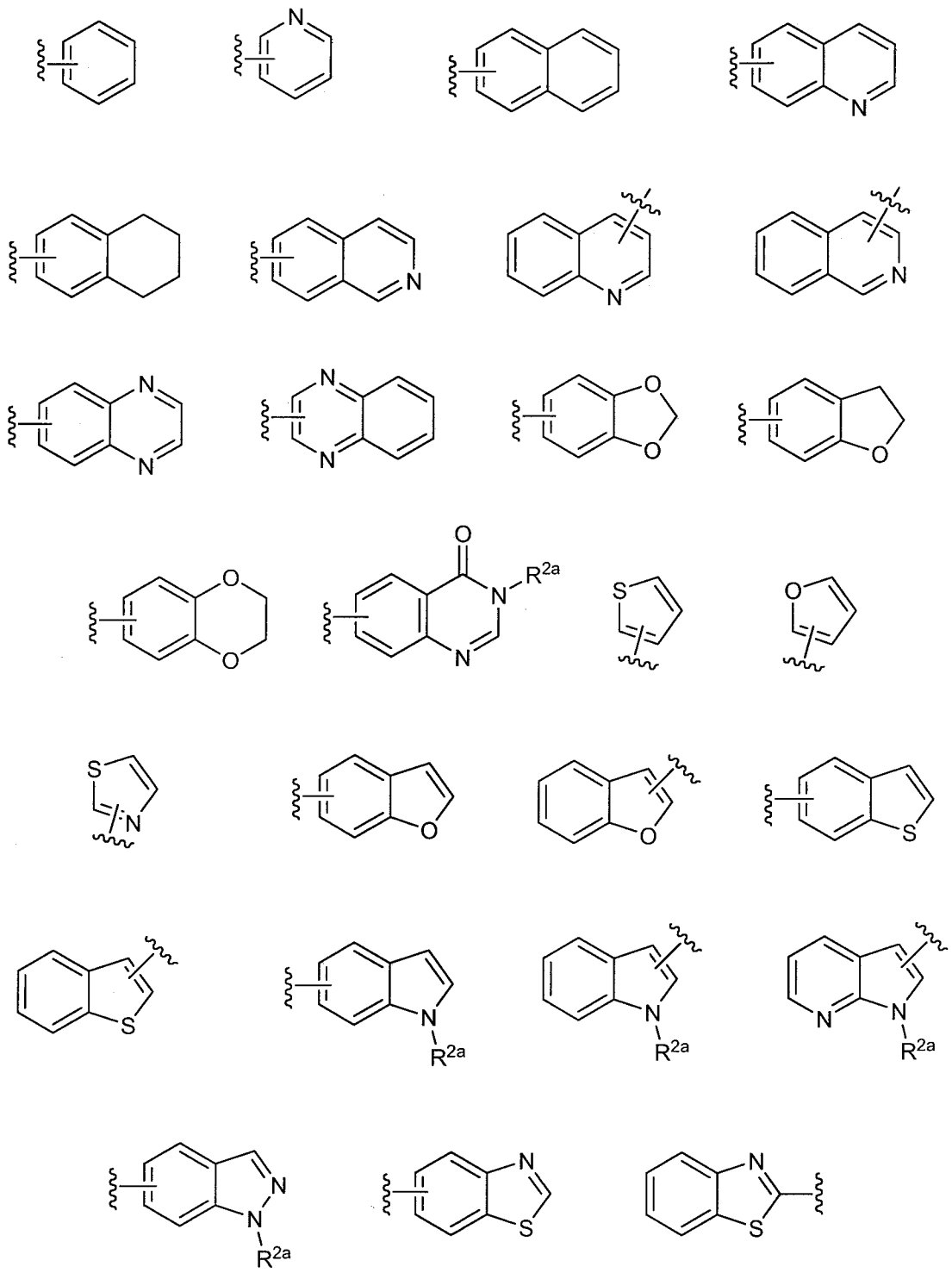
98. The compound of claim 97, wherein W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-N(R^{7b})_2$, or F; and wherein each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring; and each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

99. The compound of claim 97, wherein W is $-C(H)(N(R^{7b})_2)-$, or $-CHR^7$, wherein each occurrence of R^7 or R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

100. The compound of claim 97, wherein W is a covalent bond and G_1 is N.

101. The compound of claim 97, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

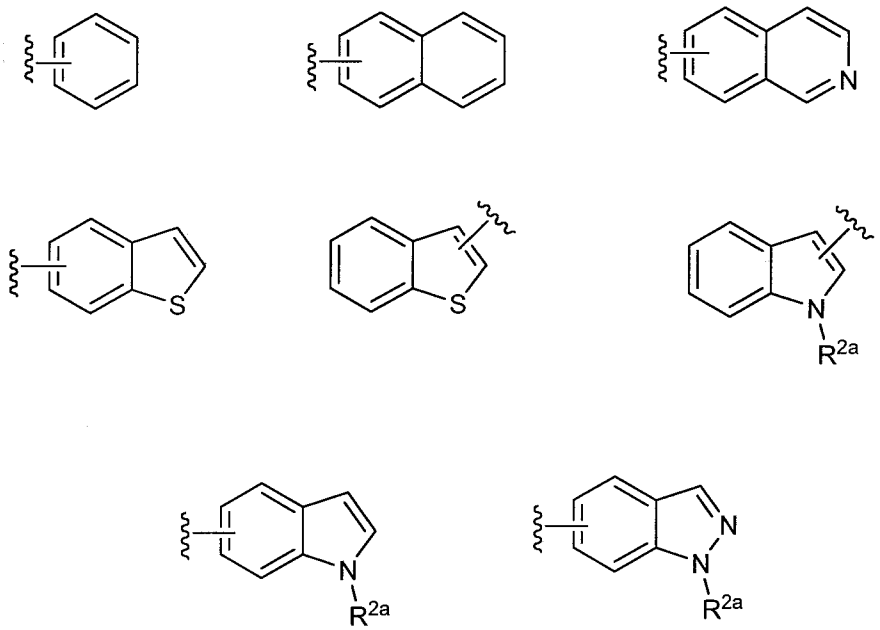
102. The compound of claim 97, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

103. The compound of claim 102, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

104. The compound of claim 97, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-C(H)(N(R^{7b})_2)-$ or $-CHR^7-$, wherein each occurrence of R^7 or R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

105. The compound of claim 104, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-CH_2-$.

106. The compound of claim 97, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -NHS(O)$_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

107. The compound of claim 106, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, -OC_{1-3} alkyl, or –OC_{1-3} haloalkyl; and n is 0 to 3.

108. The compound of claim 107, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, -OCH_3, or –OCF_3; and n is 0 to 3.

109. The compound of claim 108, wherein Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

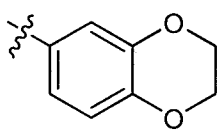
110. The compound of claim 109, wherein Ring A is a phenyl group, n is 1, and R^2 is in the para position.

111. The compound of claim 109, wherein Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions.

112. The compound of claim 101, wherein ring A is a naphthyl group, R^2 is halogen and n is 1 to 2.

113. The compound of claim 101, wherein ring A is a naphthyl group and n is 0.

114. The compound of claim 101, wherein Ring A is a 2-naphthyl group.

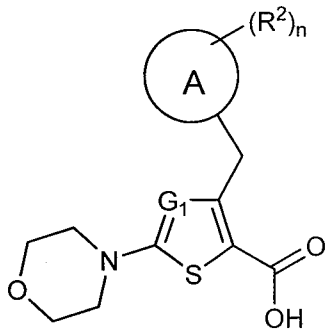
115. The compound of claim 101, wherein Ring A is .

116. The compound of claim 101, wherein Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

117. The compound of claim 101, wherein Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring.

118. The compound of claim 117, wherein Ring A is substituted with one or more C_{1-3} alkyl groups.

119. A compound having the formula **III-A**:



III-A

wherein G_1 is N or $-CR^8$, and R^8 is –CN.

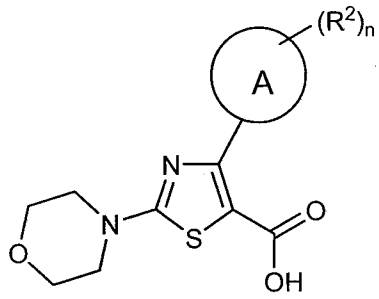
120. The compound of claim 119, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

121. The compound of claim 119, wherein:

ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

122. The compound of claim 61, wherein the compound has the formula **IV-A**:



IV-A.

123. The compound of claim 122, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

124. The compound of claim 122, wherein:

ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

125. A composition comprising a compound of any one of claims 1, 2, 24, 43, 60, 61, 97, 119 or 122, and a pharmaceutically acceptable carrier.

126. A method of treating a proliferative disorder in a patient comprising administering to said patient a therapeutically effective amount of a compound of claim 1, 2, 24, 43, 60, 61, 97, 119 or 122,.

127. The method of claim 126, further comprising administering an additional therapeutic agent..

128. The method of claim 126, further comprising administering an additional chemotherapeutic agent.

129. The method of claim 126, wherein the proliferative disorder is breast cancer, bladder cancer, colon cancer, glioma, glioblastoma, lung cancer, hepatocellular cancer, gastric cancer,

melanoma, thyroid cancer, endometrial cancer, renal cancer, cervical cancer, pancreatic cancer, esophageal cancer, prostate cancer, brain cancer, or ovarian cancer.

130. A method of treating an inflammatory or cardiovascular disorder in a patient comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1, 2, 24, 43, 60, 61, 97, 119 or 122,.

131. The method of claim 130, wherein the inflammatory or cardiovascular disorder is selected from allergies/anaphylaxis, acute and chronic inflammation, rheumatoid arthritis, autoimmunity disorders, thrombosis, hypertension, cardiac hypertrophy, and heart failure.

132. A method for inhibiting PI3K or VPS34 activity in a patient comprising administering a composition comprising a therapeutically effective amount of a compound of any one of claims 1, 2, 24, 43, 60, 61, 97, 119 or 122,.