COMPOUNDS MODULATING C-FMS AND/OR C-KIT ACTIVITY AND USES THEREFOR

RELATED PATENT APPLICATIONS

[0001] This application claims priority to U.S. Provisional App. No. 60/860,749, entitled "Compounds Modulating c-Fms and c-Kit Activity and Uses Therefor", filed November 22, 2006, and is related to U.S. Patent App. No. 11/435,381, entitled "Compounds Modulating c-Kit and c-Fms Activity and Uses Therefor", filed May 16, 2006, which claims the benefit of U.S. Provisional App. No. 60/682,063, entitled "Compounds Modulating c-Kit Activity and Uses Therefor", filed May 17, 2005, U.S. Provisional App. No. 60/682,051, entitled "Compounds Modulating c-Fms Activity and Uses Therefor", filed May 17, 2005, U.S. Provisional App. No. 60/682,042, entitled "Compounds Modulating c-Kit and c-Fms Activity and Uses Therefor", filed May 17, 2005, U.S. Provisional App. No. 60/692,750, entitled "Compounds Modulating c-Kit and c-Fms Activity and Uses Therefor", filed June 22, 2005, and U.S. Provisional App. No. 60/692,960, entitled "Compounds and Methods for Kinase Modulation, and Indications Therefor", filed June 22, 2005, all of which are incorporated herein by reference in their entireties and for all purposes.

FIELD OF THE INVENTION

[0002] This invention relates to ligands for c-fms and c-kit, and to methods for use thereof. The information provided is intended solely to assist the understanding of the reader. None of the information provided nor references cited is admitted to be prior art to the present invention. Each of the references cited is incorporated herein in its entirety and for any purpose.

BACKGROUND OF THE INVENTION

[0003] C-fms and c-kit are both type III transmembrane receptor protein tyrosine kinases (RPTKs) that regulate key signal transduction cascades that control cellular growth and proliferation. Both receptors have similar structural features comprising five extracellular immunoglobulin (IG) domains, a single transmembrane domain, and a split cytoplasmic kinase domain separated by a kinase insert segment.

c-Fms

[0004] C-fms is a member of the family of genes originally isolated from the Susan McDonough strain of feline sarcoma viruses. The cellular proto-oncogene FMS (c-fms, cellular felinc McDonough sarcoma) codes for the receptor for the macrophage colony-stimulating factor (M-CSF). C-fms is crucial for the growth and differentiation of the monocyte-macrophage lineage, and upon binding of M-CSF to the extracellular domain of c-fms, the receptor dimerizes and trans-autophosphorylates cytoplasmic tyrosine residues.

[0005] M-CSF, first described by Robinson and co-workers (Blood. 1969, 33:396-9), is a cytokine that controls the production, differentiation, and function of macrophages. M-CSF stimulates differentiation of progenitor cells to mature monocytes, and prolongs the survival of monocytes. Furthermore, M-CSF enhances cytotoxicity, superoxide production, phagocytosis, chemotaxis, and secondary cytokine production of additional factors in monocytes and macrophages. Examples of such additional factors include granulocyte colony stimulating factor (G-CSF), interleukin-6 (IL-6), and interleukin-8 (IL-8). M-CSF stimulates hematopoiesis, promotes differentiation and proliferation of osteoclast progenitor cells, and has profound effects on lipid metabolism. Furthermore, M-CSF is important in pregnancy. Physiologically, large amounts of M-CSF are produced in the placenta, and M-CSF is believed to play an essential role in trophoblast differentiation (Motoyoshi, Int J Hematol. 1998, 67:109-22). The elevated serum levels of M-CSF in early pregnancy may participate in the immunologic mechanisms responsible for the maintenance of the pregnancy (Flanagan & Lader, Curr Opin Hematol. 1998, 5:181-5).

[0006] Related to c-fms and c-kit are two platelet-derived growth factor receptors, alpha (i.e., pdgfra) and beta (pdgfrb) (PDGF). The gene coding for pdgfra is located on chromosome 4q11-q12 in the same region of chromosome 4 as the oncogene coding for c-kit. The genes coding for pdgfra and c-fms appear to have evolved from a common ancestral gene by gene duplication, inasmuch as these two genes are tandemly linked on chromosome 5. They are oriented head-to-tail with the 5-prime exon of the c-fms gene located only 500 bp from the last 3-prime exon of the gene coding for pdgfra. Most gastrointestinal stromal tumors (GIST) have activating mutations in c-kit, and most patients with GISTs respond well to Gleevec, which inhibits c-kit. Heinrich et al. (Science 2003, 299:708-10) have shown that approximately 35% of GISTs lacking c-kit mutations have intragenic activation mutations in the gene encoding pdgfra, and that tumors expressing c-kit or pdgfra are indistinguishable with respect to activation of downstream signaling intermediates and cytogenetic changes associated with tumor progression. Thus, c-kit and pdgfra mutations appear to be alternative and mutually exclusive oncogenic mechanisms in GISTs.

[0007] Similarly, the observation that production of M-CSF, the major macrophage growth factor, is increased in tissues during inflammation points out a role for c-fms in diseases, such as for example inflammatory diseases. More particularly, because elevated levels of M-CSF are found in the disease state, modulation of the activity of c-fms can ameliorate disease associated with increased levels of M-CSF.

c-Kit

[0008] The Stem Cell Factor (SCF) receptor c-kit plays an important role in the development of melanocytes and mast, germ and hematopoietic cells. Stem Cell Factor (SCF) is a protein encoded by the Sl locus, and has also been called "kit ligand" (KL) and mast cell growth factor (MGF), based on the biological properties used to identify it (reviewed in Tsujimura, Pathol Int 1996, 46:933-938; Loveland, et al., J. Endocrinol 1997, 153:337-344; Vliagoftis, et al., Clin Immunol 1997, 100:435-440; Broudy, Blood 1997, 90:1345-1364; Pignon, Hermatol Cell Ther 1997, 39:114-116; and Lyman, et al., Blood 1998, 91:1101-1134.). Herein the abbreviation SCF refers to the physiological ligand for c-kit.

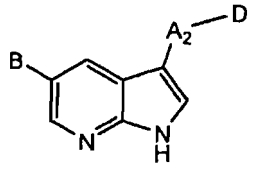
[0009] SCF is synthesized as a transmembrane protein with a molecular weight of 220 or 248 Dalton, depending on alternative splicing of the mRNA to encode exon 6. The larger protein can be proteolytically cleaved to form a soluble, glycosylated protein which noncovalently dimerizes. Both the soluble and membrane-bound forms of SCF can bind to and activate c-kit. For example, in the skin, SCF is predominantly expressed by fibroblasts, keratinocytes, and endothelial cells, which modulate the activity of melanocytes and mast cells expressing c-kit. In bone, marrow stromal cells express SCF and regulate hematopoiesis of c-kit expressing stem cells. In the gastrointestinal tract, intestinal epithelial cells express SCF and affect the interstitial cells of Cajal and intraepithelial lymphocytes. In the testis, sertoli cells and granulosa cells express SCF which regulates spermatogenesis by interaction with c-kit on germ cells.

SUMMARY OF THE INVENTION

[0010] The present invention relates to compounds active on c-fms, c-kit, or both c-fms and c-kit. In accordance with one aspect of the present invention, it has been discovered that in the treatment of diseases amenable to treatment by an effective amount of a modulator of either c-fms alone or c-kit alone, the efficacy of treatment can be enhanced if said compounds are dual inhibitors of both c-fms and c-kit. In another aspect of the present invention, compounds active on c-fms, c-kit, or both c-fms and c-kit are also active on one or more of TrkA, TrkB and HGK. In particular, the invention provides compounds of Formula II, and all sub-generic formulae thereof

(e.g. Formula IIa, IIb, IIe, IIg and IIp), Formula III, or additional compounds as described in the synthetic examples, as well as methods of using such compounds as described below. Thus, the invention provides methods of using compounds that can be used therapeutically and/or prophylactically involving modulation of c-fms, c-kit, or both c-fms and c-kit, or involving one or more of TrkA, TrkB and HGK in addition to c-fms, c-kit, or both c-fms and c-kit.

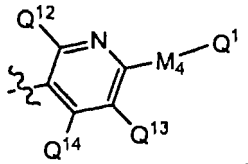
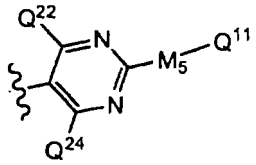
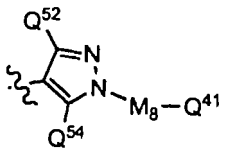
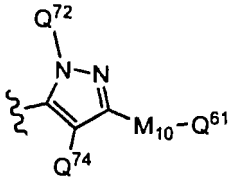
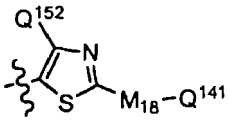
[0011] The compounds of Formula II have the following structure:



Formula II

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

D has a structure selected from the group consisting of , , , , and 

in which  indicates the attachment point of D to A_2 of Formula II;

A_2 is $-CH_2-$ or -C(O)-;

B is selected from the group consisting of hydrogen, -CN, $-OR^{41}$, $-SR^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, $-C(O)NR^{39}R^{41}$, $-C(O)R^{41}$, $-S(O)_2NR^{39}R^{41}$, $-S(O)_2R^{41}$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and

heteroaryl as B, or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

M_4 is $-NR^{39}CH_2-$, $-NR^{39}CH(R^{40})-$, $-NR^{39}CH_2CH_2-$, or $-NR^{39}C(O)-$;

M_5, M_{10}, and M_{18} are selected from the group consisting of a bond, $-NR^{39}-$, -S-, -O-, $-NR^{39}CH_2-$, $-NR^{39}CH_2CH_2-$, $-NR^{39}CH(R^{40})-$, $-SCH_2-$, $-OCH_2-$, $-C(O)NR^{39}-$, $-S(O)_2NR^{39}-$, $-CH_2NR^{39}-$, $-CH(R^{40})NR^{39}-$, $-NR^{39}C(O)-$, and $-NR^{39}S(O)_2-$;

M_8 is selected from the group consisting of a bond, $-CH_2-$, $-CH_2C(O)-$, $-S(O)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2CH_2CH_2-$, $-S(O)_2NR^{39}-$, $-S(O)_2NR^{39}CH_2-$, $-S(O)_2NR^{39}CH(CH_3)-$, $-S(O)_2NR^{39}CH_2CH_2-$, $-C(O)-$, $-C(O)CH_2-$, $-C(O)CH(CH_3)-$, $-C(O)CH_2CH_2-$, $-C(O)NR^{39}-$, $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(CH_3)-$, and $-C(O)NR^{39}CH_2CH_2-$;

Q^1 is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of $-OR^{41}$, $-SR^{41}$, $-S(O)R^{41}$, $-S(O)_2R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as a substituent of Q^1 or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

Q^{11}, Q^{41}, Q^{61}, and Q^{141} are lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein lower alkyl is optionally substituted with one or more fluoro, lower alkoxy, or fluoro substituted lower alkoxy, and wherein cyclaolkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of $-OR^{41}$, $-SR^{41}$, $-S(O)R^{41}$, $-S(O)_2R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-NR^{39}C(O)R^{41}$, $-NR^{39}S(O)_2R^{41}$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as a substituent of Q^{11}, Q^{41}, Q^{61}, or Q^{141}, or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of

-OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^{42}, -SR^{42}, -NHR^{42}, -$NR^{42}R^{42}$, -$NR^{39}C(O)R^{42}$, -$NR^{39}S(O)_2R^{42}$, -$S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

Q^{12} is fluoro, chloro or -CF_3;

Q^{13} and Q^{14} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl;

Q^{22}, Q^{24}, Q^{52}, and Q^{54} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, -$NR^{44}R^{44}$, -OR^{44}, and -SR^{44}, provided, however, that at least one of Q^{22} and Q^{24} and at least one of Q^{52} and Q^{54} is hydrogen, fluoro, chloro, lower alkyl or fluoro substituted lower alkyl;

Q^{74} and Q^{152} are hydrogen, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, -$NR^{44}R^{44}$, -OR^{44}, or –SR^{44};

Q^{72} is hydrogen, lower alkyl or fluoro substituted lower alkyl;

R^{39} at each occurrence is independently hydrogen or lower alkyl;

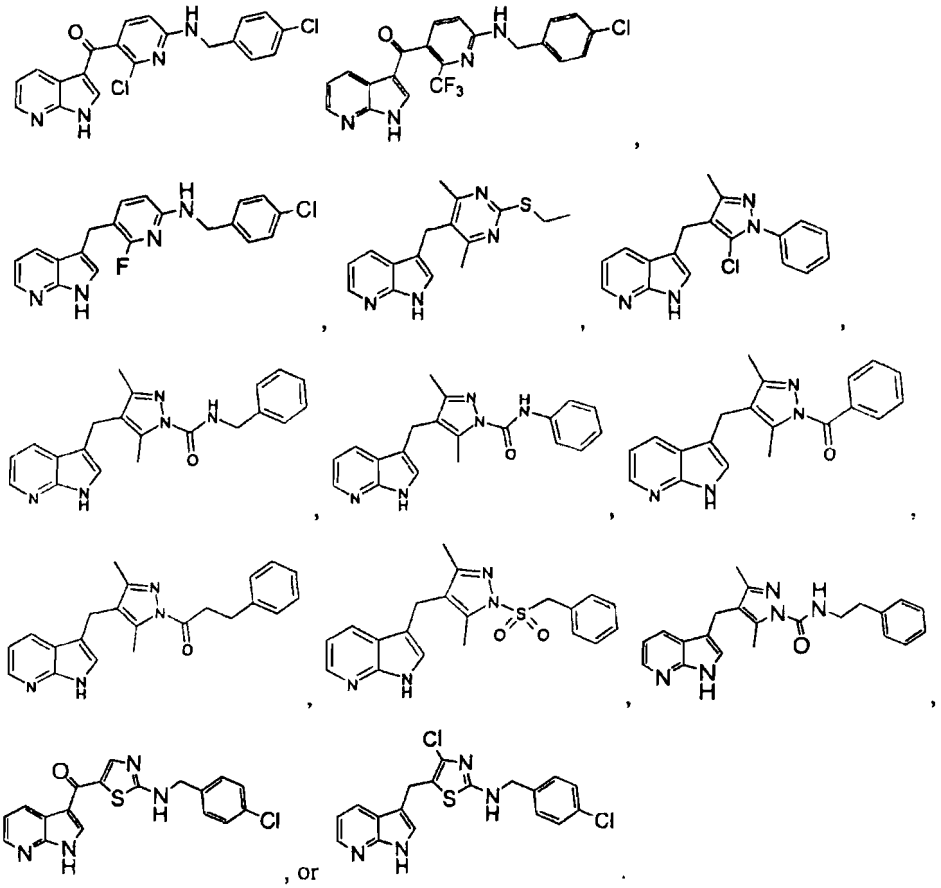
R^{40} is lower alkyl or fluoro substituted lower alkyl;

R^{41} at each occurrence is independently selected from the group consisting of lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{41} or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^{42}, -SR^{42}, -NHR^{42}, -$NR^{42}R^{42}$, -$NR^{39}C(O)R^{42}$, -$NR^{39}S(O)_2R^{42}$, -$S(O)_2R^{42}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

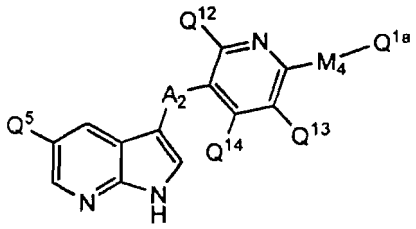
R^{42} at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein heterocycloalkyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy and fluoro substituted lower alkoxy; and

each R^{44} is independently hydrogen, lower alkyl or fluoro substituted lower alkyl;

provided, however, that the compound is not



[0012] In one embodiment, a compound of Formula II has a structure according to the following sub-generic structure, Formula IIa,



Formula IIa,

all salts, prodrugs, tautomers, and isomers thereof,

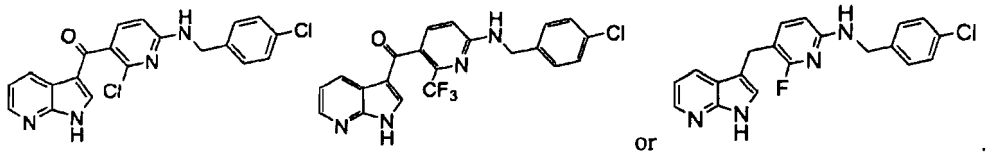
wherein:

Q^{1a} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$;

Q^5 is hydrogen, -CN, -OR^{41}, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, and -OR^{41}; and

A_2, M_4, Q^{12}, Q^{13}, Q^{14} and R^{41} are as defined for Formula II;

provided, however, that the compound is not



or

.

[0013] In one embodiment of compounds of Formula IIa, A_2 is -CH_2- and M_4 is -$NHCH_2$-. In one embodiment A_2 is -C(O)- and M_4 is -$NHCH_2$-. In one embodiment A_2 is -C(O)- and M_4 is -NHC(O)-. In one embodiment A_2 is -CH_2- and M_4 is -NHC(O)-.

[0014] In one embodiment of compounds of Formula IIa, A_2 is -CH_2-, M_4 is -$NHCH_2$-, Q^5 is -OR^{41}, -CN, C_{1-3} alkyl, fluoro substituted C_{1-3} alkyl, fluoro, chloro, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{13} and Q^{14} are hydrogen.

[0015] In one embodiment of compounds of Formula IIa, A_2 is -C(O)-, M_4 is -$NHCH_2$-, Q^5 is -OR^{41}, -CN, C_{1-3} alkyl, fluoro substituted C_{1-3} alkyl, fluoro, chloro, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{13} and Q^{14} are hydrogen.

[0016] In one embodiment of compounds of Formula IIa, A_2 is -C(O)-, M_4 is -NHC(O)-, Q^5 is -OR^{41}, -CN, C_{1-3} alkyl, fluoro substituted C_{1-3} alkyl, fluoro, chloro, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{13} and Q^{14} are hydrogen.

[0017] In one embodiment of compounds of Formula IIa, A_2 is -CH_2-, M_4 is -NHC(O)-, Q^5 is -OR^{41}, -CN, C_{1-3} alkyl, fluoro substituted C_{1-3} alkyl, fluoro, chloro, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{13} and Q^{14} are hydrogen.

[0018] In one embodiment, further to any of the embodiments of Formula IIa above, R^{41} is R^{42} as defined for Formula II.

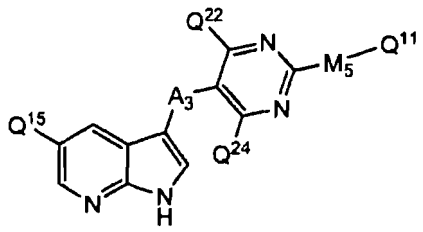
[0019] In one embodiment, further to any of the embodiments of Formula IIa above, Q^{1a} is phenyl or pyridinyl, wherein phenyl or pyridinyl are substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, methyl, methoxy, trifluoromethyl, difluoromethoxy and trifluoromethoxy; A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; and Q^5 is -CN, fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy. In one embodiment, further to any of the embodiments of Formula IIa above, Q^{1a} is phenyl mono substituted with chloro, preferably at the 4-position; A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; and Q^5 is -CN, fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy. In one embodiment, further to any of the embodiments of Formula IIa, Q^{1a} is pyridin-3-yl monosubstituted with methyl, methoxy, trifluoromethyl, difluoromethoxy or trifluoromethoxy, preferably at the 6-position; A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; Q^5 is -CN, fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy.

[0020] In one embodiment of compounds of Formula IIa, A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; Q^{1a} is phenyl or pyridinyl, wherein phenyl or pyridinyl are substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, methyl, methoxy, trifluoromethyl, difluoromethoxy and trifluoromethoxy; Q^5 is hydrogen, fluoro, chloro, methyl, methoxy, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -CN, or 1-methyl-1H-pyrazole-4-yl; Q^{12} is fluoro or chloro; and Q^{13} and Q^{14} are hydrogen. In one embodiment, A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; Q^{1a} is phenyl mono substituted with chloro, preferably at the 4-position; Q^5 is hydrogen, chloro, methyl, methoxy, or -CN; Q^{12} is fluoro or chloro; and Q^{13} and Q^{14} are hydrogen. In one embodiment, A_2 is $-CH_2-$; M_4 is $-NHCH_2-$; Q^{1a} is pyridin-3-yl monosubstituted with methyl, methoxy, trifluoromethyl, difluoromethoxy or trifluoromethoxy, preferably at the 6-position; Q^5 is hydrogen, chloro, methyl, methoxy, -CN, or 1-methyl-1H-pyrazole-4-yl; Q^{12} is fluoro or chloro; and Q^{13} and Q^{14} are hydrogen.

[0021] In one embodiment of compounds of Formula IIa, the compound is selected from the group consisting of:

(4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-amine **(P-0132)**,
(4-Chloro-benzyl)-[6-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0161)**,
[6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0174)**,
[6-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0176)**,
{6-Chloro-5-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0179)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0186)**,
[6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0187)**,
[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0188)**,
3-{2-Chloro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0232)**,
[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0233)**,
[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0234)**,
[6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **(P-0378)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **(P-0379)**,
(5-Fluoro-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0414)**,
3-{2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0415)**,
3-[6-(4-Chloro-benzylamino)-2-fluoro-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0432)**, and
all salts, prodrugs, tautomers, and isomers thereof.

[0022] In one embodiment, a compound of Formula II has a structure according to the following sub-generic structure, Formula IIb,



Formula IIb,

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A_3 is $-CH_2-$ or -C(O)-;

Q^{15} is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$; and

M_5, Q^{11}, Q^{22}, Q^{24}, and R^{41}, are as defined for Formula II.

[0023] In one embodiment of compounds of Formula IIb, M_5 is $-NR^{39}CH_2-$, $-NR^{39}CH(R^{40})-$, $-NR^{39}CH_2CH_2-$, or $-NR^{39}C(O)-$; A_3 is $-CH_2-$ or -C(O)-, preferably $-CH_2-$; Q^{11} is cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; Q^{15} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; and Q^{22} and Q^{24} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl, preferably hydrogen, fluoro, chloro, or $-CF_3$, more preferably both Q^{22} and Q^{24} are hydrogen; wherein R^{41} is as defined for Formula II.

[0024] In one embodiment, further to any of the embodiments of Formula IIb above, R^{41} is R^{42} as defined for Formula II.

[0025] In one embodiment of compounds of Formula IIb, M_5 is $-NHCH_2CH_2-$, $-NHCH_2-$ $-N(CH_3)CH_2-$, or $-NHCH(CH_3)-$, preferably $-NHCH_2-$; A_3 is $-CH_2-$; Q^{11} is cycloalkyl, heterocycloalkyl, phenyl or heteroaryl, wherein phenyl or heteroaryl are optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, lower alkyl, fluoro

substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, di-alkylamino, and heterocycloalkyl; Q^{15} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and Q^{22} and Q^{24} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl, preferably hydrogen, fluoro, chloro, or $-CF_3$, more preferably both Q^{22} and Q^{24} are hydrogen.

[0026] In one embodiment of compounds of Formula IIb, M_5 is $-NHCH_2-$; A_3 is $-CH_2-$; Q^{11} is phenyl substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, methyl, fluoro substituted methyl, methoxy, and fluoro substituted methoxy; Q^{15} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, preferably hydrogen or chloro; and Q^{22} and Q^{24} are hydrogen.

[0027] In one embodiment of compounds of Formula IIb, the compound is selected from the group consisting of:
(4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0260)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,6-difluoro-benzyl)-amine **(P-0261)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine **(P-0262)**,
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **(P-0263)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-benzyl)-amine **(P-0264)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,4-difluoro-benzyl)-amine **(P-0265)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine **(P-0266)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,5-difluoro-benzyl)-amine **(P-0267)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-trifluoromethyl-benzyl)-amine **(P-0268)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-5-trifluoromethyl-

benzyl)-amine (**P-0289**),
(2-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0291**),
(2,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0292**),
(2-Chloro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0293**),
(3-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0294**),
(3,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0295**),
(2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0300**),
(2-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0301**),
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0302**),
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethoxy-benzyl)-amine (**P-0303**),
(5-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0304**),
(2,4-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0305**),
(2,4-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0306**),
(4-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0307**),
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine (**P-0308**),
(2-Fluoro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0309**),
(2,5-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0310**),
(3-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0311**),
(2-Difluoromethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0312**),
(2,3-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0313**),
(4-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0314**),
(5-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0315**),
(2-Chloro-4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0316**),

(5-Chloro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0317**),

(5-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0318**),

(2-Fluoro-4-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0319**),

(4-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0320**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-difluoromethoxy-benzyl)-amine (**P-0390**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-trifluoromethyl-benzyl)-amine (**P-0391**),

(3-Chloro-2-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0392**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-3-trifluoromethyl-benzyl)-amine (**P-0393**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-4-trifluoromethyl-benzyl)-amine (**P-0394**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,3-difluoro-benzyl)-amine (**P-0395**),

(2-Chloro-4-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0396**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethoxy-benzyl)-amine (**P-0402**),

(2-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0407**),

(2-Chloro-5-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0408**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-4-ylmethyl-amine (**P-0416**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-pyrrolidin-1-yl-ethyl)-amine (**P-0417**),

Benzyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0418**),

Benzyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0419**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethoxy-benzyl)-

amine (**P-0420**),
(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0421**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-3-ylmethyl-amine (**P-0422**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-fluoro-benzyl)-amine (**P-0423**),
(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0424**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3,5-difluoro-benzyl)-amine (**P-0425**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[1-(2-fluoro-phenyl)-ethyl]-amine (**P-0426**),
[1-(4-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0427**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[(S)-1-(4-fluoro-phenyl)-ethyl]-amine (**P-0428**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0429**),
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0430**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methyl-benzyl)-amine (**P-0431**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-benzyl)-amine (**P-0433**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-morpholin-4-yl-ethyl)-amine (**P-0434**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclohexylmethyl-amine (**P-0435**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-2-ylmethyl-amine (**P-0436**),
[2-(4-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0437**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-difluoromethoxy-benzyl)-amine (**P-0438**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methoxy-benzyl)-amine

(**P-0439**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-benzyl)-amine (**P-0440**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-ethyl)-amine (**P-0441**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-benzyl)-amine (**P-0442**),

(3-Chloro-4-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0443**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-ethoxy-benzyl)-amine (**P-0444**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-morpholin-4-yl-benzyl)-amine (**P-0445**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-difluoromethoxy-benzyl)-amine (**P-0446**),

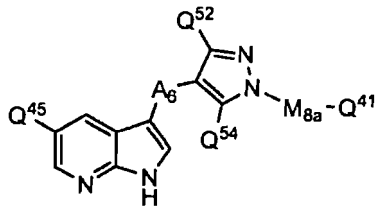
(4-Chloro-3-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0447**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[1-(3-fluoro-phenyl)-ethyl]-amine (**P-0448**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-dimethylamino-benzyl)-amine (**P-0449**), and

all salts, prodrugs, tautomers, and isomers thereof.

[0028] In one embodiment, a compound of Formula II has a structure according to the following sub-generic structure, Formula IIe,



Formula IIe,

all salts, prodrugs, tautomers, and isomers thereof,

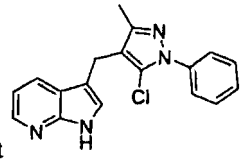
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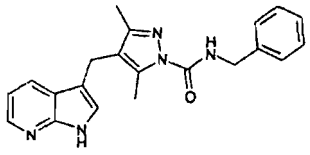
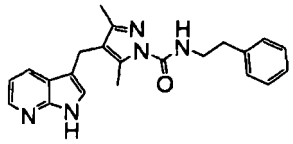
A_6 is $-CH_2-$ or $-C(O)-$;

M_{8a} is $-CH_2-$, $-CH_2C(O)-$, $-C(O)NR^{39}CH_2-$, $-C(O)NR^{39}CH(R^{40})-$, or $-C(O)NR^{39}CH_2CH_2-$;

Q^{45} is hydrogen, -CN, -OR^{41}, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, and -OR^{41}; and

Q^{41}, Q^{52}, Q^{54}, R^{39}, R^{40}, and R^{41} are as defined for Formula II;

provided, however, that the compound is not ,

, or .

[0029] In one embodiment of compounds of Formula IIe, M_{8a} is -$C(O)NR^{39}CH_2$-, -$C(O)NR^{39}CH(CH_3)$-, or -$C(O)NR^{39}(CH_2)_2$-; A_6 is -CH_2- or -C(O)-, preferably -CH_2-; Q^{41} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; Q^{45} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{52} and Q^{54} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl, preferably Q^{52} and Q^{54} are independently hydrogen, fluoro, chloro, methyl, or -CF_3; wherein R^{41} is as defined in Formula II.

[0030] In one embodiment, further to any of the embodiments of Formula IIe above, R^{41} is R^{42} as defined for Formula II.

[0031] In one embodiment of compounds of Formula IIe, M_{8a} is -$C(O)NHCH_2$-, -$C(O)NHCH(CH_3)$- or -$C(O)NH(CH_2)_2$-; A_6 is -CH_2- or -C(O)-, preferably -CH_2-; Q^{41} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, methyl, fluoro substituted methyl, methoxy, and fluoro substituted methoxy; Q^{45} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy, preferably hydrogen or chloro; and Q^{52} and

Q^{54} are independently hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl, preferably Q^{52} and Q^{54} are methyl.

[0032] In one embodiment of compounds of Formula IIe, the compound is selected from the group consisting of:

3-(1-Benzyl-3,5-dimethyl-1H-pyrazol-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **(P-0133)**,

2-[3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazol-1-yl]-1-phenyl-ethanone **(P-0134)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methoxy-benzylamide **(P-0135)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-chloro-benzylamide **(P-0136)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-fluoro-benzylamide **(P-0137)**,

3-[3,5-Dimethyl-1-(5-trifluoromethyl-furan-2-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine **(P-0138)**,

3-[3,5-Dimethyl-1-(5-methyl-isoxazol-3-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine **(P-0139)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-chloro-benzylamide **(P-0140)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(4-methoxy-phenyl)-ethyl]-amide **(P-0141)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 3-methoxy-benzylamide **(P-0142)**,

3-{3,5-Dimethyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyl]-1H-pyrazol-4-ylmethyl}-1H-pyrrolo[2,3-b]pyridine **(P-0143)**,

3-[3,5-Dimethyl-1-(4-methyl-2-phenyl-thiazol-5-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine **(P-0144)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-methoxy-benzylamide **(P-0145)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide **(P-0146)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide **(P-0147)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(2-fluoro-phenyl)-ethyl]-amide **(P-0148)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid ((S)-1-phenyl-ethyl)-amide **(P-0149)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 3-fluoro-benzylamide **(P-0150)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-fluoro-benzylamide **(P-0151)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methyl-benzylamide **(P-0152)**,

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-methyl-benzylamide **(P-0153)**,

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide **(P-0157)**,

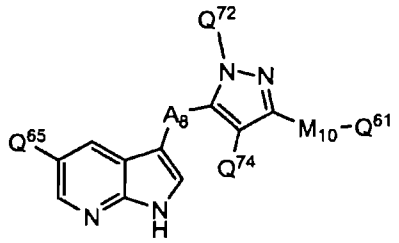
4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid 4-fluoro-benzylamide **(P-0158)**,

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid 4-chloro-benzylamide **(P-0159)**,

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid [(S)-1-(4-fluoro-phenyl)-ethyl]-amide **(P-0160)** , and

all salts, prodrugs, tautomers, and isomers thereof.

[0033] In one embodiment, a compound of Formula II has a structure according to the following sub-generic structure, Formula IIg,



Formula IIg,

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A_8 is $-CH_2-$, or $-C(O)-$;

Q^{65} is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the

group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, and -OR^{41}; and

M_{10}, Q^{61}, Q^{72}, Q^{74}, and R^{41} are as defined for Formula II.

[0034] In one embodiment of compounds of Formula IIg, M_{10} is -$NR^{39}CH_2$- or -NR^{39}-$(CH_2)_2$-; A_8 is -CH_2- or -C(O)-, preferably -CH_2-; Q^{61} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; Q^{65} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NHR^{41}, -$NR^{41}R^{41}$, -OR^{41} and -$S(O)_2R^{41}$; and Q^{74} is hydrogen, fluoro, chloro, lower alkyl or fluoro substituted lower alkyl, wherein R^{41} is as defined for Formula II.

[0035] In one embodiment, further to any of the embodiments of Formula IIg above, R^{41} is R^{42} as defined for Formula II.

[0036] In one embodiment of compounds of Formula IIg, M_{10} is -$NHCH_2$-; A_8 is -CH_2-; Q^{61} is phenyl optionally substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy or trifluoromethoxy; Q^{65} is hydrogen, fluoro, -CN, or 1-methyl-pyrazol-4-yl; Q^{72} is lower alkyl or fluoro substituted lower alkyl; and Q^{74} is hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl. In one embodiment, M_{10} is -$NHCH_2$-; A_8 is -CH_2-; Q^{61} is 4-fluoro-phenyl; Q^{65} is hydrogen, chloro, -CN, or 1-methyl-pyrazol-4-yl; Q^{72} is methyl or ethyl; and Q^{74} is hydrogen or chloro.

[0037] In one embodiment, the compound of Formula IIg is selected from the group consisting of:

[1-Ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **(P-0165)**,

(4-Fluoro-benzyl)-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-amine **(P-0169)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **(P-0170)**,

(4-Fluoro-benzyl)-{1-methyl-5-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-1H-pyrazol-3-yl}-amine **(P-0180)**,

(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-

methanone **(P-0184)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-ethyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **(P-0185)**,

3-[5-(4-Fluoro-benzylamino)-2-methyl-2H-pyrazol-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0191)**,

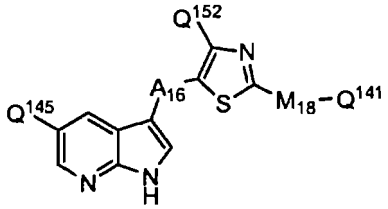
(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-amine **(P-0410)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(2,5-difluoro-benzyl)-amine **(P-0411)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(2-fluoro-benzyl)-amine **(P-0413)**, and

all salts, prodrugs, tautomers, and isomers thereof.

[0038] In one embodiment, a compound of Formula II has a structure according to the following sub-generic structure, Formula IIp,



Formula IIp,

all salts, prodrugs, tautomers, and isomers thereof,

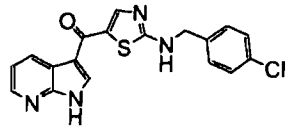
wherein:

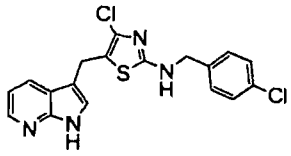
A_{16} is $-CH_2-$ or -C(O)-;

Q^{145} is hydrogen, -CN, $-OR^{41}$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, and $-OR^{41}$;

Q^{152} is hydrogen, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy; and

M_{18}, Q^{141}, and R^{41}, are as defined for Formula II;

provided, however, that the compound is not  or



[0039] In one embodiment of compounds of Formula IIp, M_{18} is $-NR^{39}CH_2-$ or $-NR^{39}-(CH_2)_2-$; A_{16} is $-CH_2-$ or -C(O)-, preferably $-CH_2-$; Q^{141} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; Q^{145} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; and Q^{152} is hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl; wherein R^{41} is as defined for Formula II.

[0040] In one embodiment of compounds of Formula IIp, M_{18} is $-NH-CH_2-$ or $-NH-(CH_2)_2-$, preferably $-NH-CH_2-$; A_{16} is $-CH_2-$ or -C(O)-, preferably $-CH_2-$; Q^{141} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, and heterocycloalkyl; Q^{145} is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy, preferably hydrogen, -CN, or chloro; and Q^{152} is hydrogen, fluoro, chloro, lower alkyl, or fluoro substituted lower alkyl, preferably hydrogen or chloro, more preferably chloro.

[0041] In one embodiment, the compound of Formula Ih is selected from the group consisting of
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **(P-0156)**,
[4-Ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **(P-0162)**,
(4-Fluoro-benzyl)-[4-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **(P-0163)**,
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine **(P-0164)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-2-ylmethyl-amine **(P-0167)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine **(P-0168)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-amine **(P-0171)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(1,5-dimethyl-1H-pyrazol-3-ylmethyl)-amine **(P-0172)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **(P-0173)**,

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-amine**(P-0175)**,

[2-(4-Fluoro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **(P-0177)**,

{2-[(4-Chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **(P-0178)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-thiazol-2-ylmethyl-amine **(P-0189)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **(P-0190)**,

Benzyl-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **(P-0192)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-methoxy-benzyl)-amine **(P-0193)**,

(4-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **(P-0194)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **(P-0195)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-dimethyl-thiazol-5-ylmethyl)-amine **(P-0196)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-5-methyl-3H-imidazol-4-ylmethyl)-amine **(P-0197)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-2H-pyrazol-3-ylmethyl)-amine **(P-0198)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl)-amine **(P-0199)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-fluoro-pyridin-4-ylmethyl)-amine **(P-0200)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methyl-thiazol-4-ylmethyl)-amine (**P-0201**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-methyl-thiazol-5-ylmethyl)-amine (**P-0202**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-chloro-pyridin-2-ylmethyl)-amine (**P-0203**),
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-dimethyl-thiazol-5-ylmethyl)-amine (**P-0204**),
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-5-methyl-3H-imidazol-4-ylmethyl)-amine (**P-0205**),
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine (**P-0206**),
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-methoxy-pyridin-3-ylmethyl)-amine (**P-0207**),
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4,5-dimethyl-thiophen-2-ylmethyl)-amine (**P-0208**),
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,5-dimethyl-thiophen-3-ylmethyl)-amine (**P-0209**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**P-0231**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine (**P-0236**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine (**P-0237**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-chloro-pyridin-4-ylmethyl)-amine (**P-0238**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(1-ethyl-1H-pyrazol-4-ylmethyl)-amine (**P-0239**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine (**P-0240**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-methoxy-pyridin-3-ylmethyl)-amine (**P-0241**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0242**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-chloro-6-fluoro-benzyl)-amine (**P-0243**),

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-phenethyl-amine **(P-0244)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-difluoro-benzyl)-amine **(P-0245)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-fluoro-benzyl)-amine **(P-0246)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine **(P-0247)**,

(2-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **(P-0248)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methyl-benzyl)-amine **(P-0249)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-chloro-4-fluoro-benzyl)-amine **(P-0250)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-fluoro-pyridin-2-ylmethyl)-amine **(P-0251)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-morpholin-4-yl-pyridin-2-ylmethyl)-amine **(P-0252)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3,5-dichloro-pyridin-4-ylmethyl)-amine **(P-0253)**,

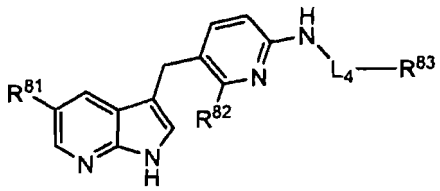
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-trifluoromethyl-benzyl)-amine **(P-0254)**,

[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-amine **(P-0255)**,

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **(P-0290)** , and

all salts, prodrugs, tautomers, and isomers thereof.

[0042] The compounds of Formula III have the following structure:



Formula III,

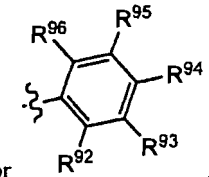
all salts, prodrugs, tautomers, and isomers thereof,

wherein:

L_4 is $-CH_2-$, $-CH_2CH_2-$, $-CH(R^{40})-$, -C(O)- or -C(O)NH-;

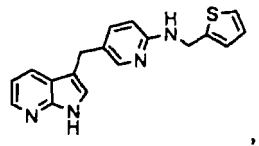
R^{81} is selected from the group consisting of hydrogen, $-OR^{41}$, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$;

R^{82} is selected from the group consisting of hydrogen, C_{1-3} alkyl, fluoro substituted C_{2-3} alkyl, OH, C_{1-3} alkoxy, and fluoro substituted C_{1-3} alkoxy;

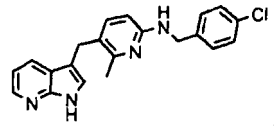
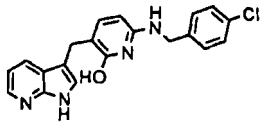
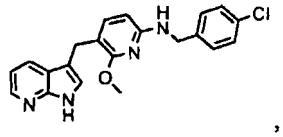
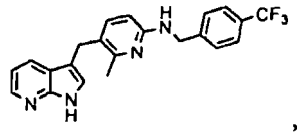
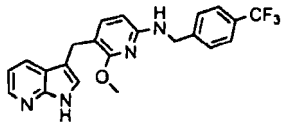
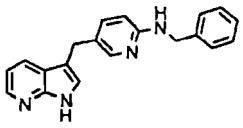
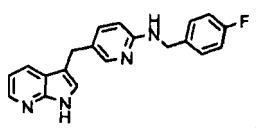
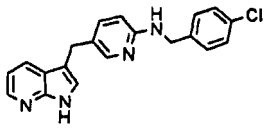
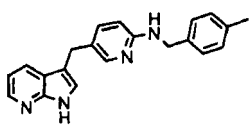
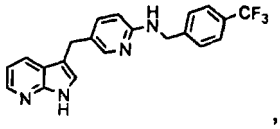
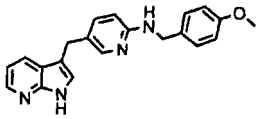
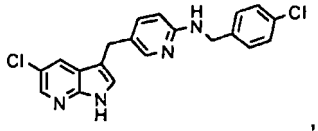
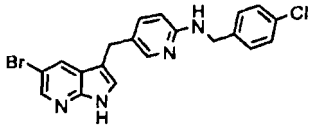
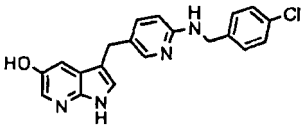
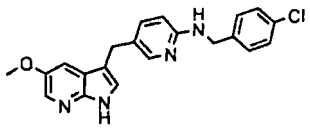
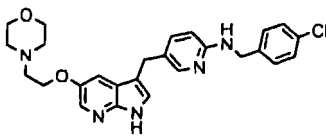
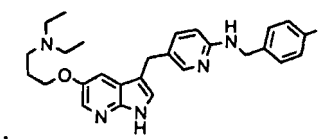
R^{83} is heterocycloalkyl, heteroaryl, or  , in which  indicates the attachment point of R^{83} to L_4 of Formula III, wherein heterocycloalkyl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$;

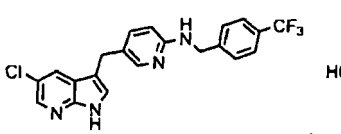
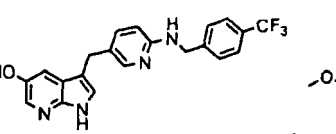
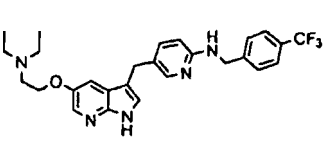
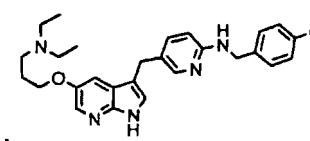
R^{92}, R^{93}, R^{94}, R^{95}, and R^{96} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, $-NHS(O)_2R^{41}$, $-NHC(O)R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$; and

R^{40} and R^{41} are as defined for Formula II;



provided, however, that the compound is not

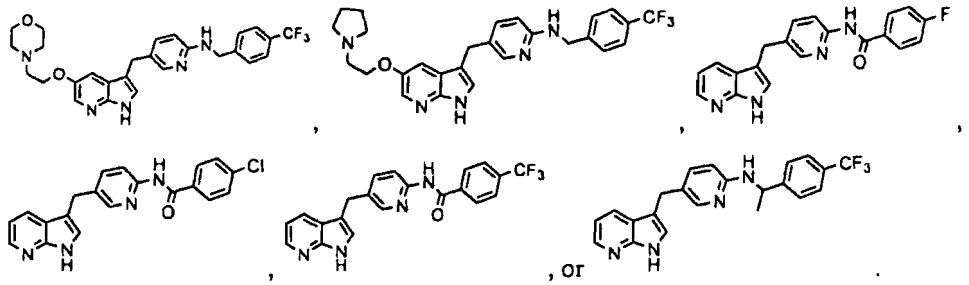

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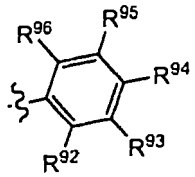
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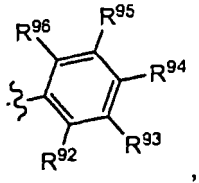
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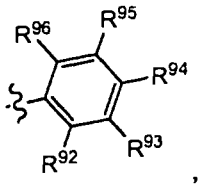
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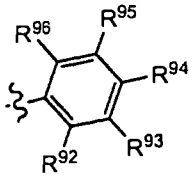
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[0043] In one embodiment of compounds of Formula III, L_4 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or $-C(O)-$; R^{81} is hydrogen, fluoro, chloro, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy; R^{82} is hydrogen; R^{83} is  , wherein R^{92}, R^{93}, R^{94}, R^{95}, and R^{96} are independently hydrogen, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy, provided, however, that when R^{94} is fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy, at least one of R^{92}, R^{93}, R^{95}, and R^{96} is fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy.

[0044] In one embodiment of compounds of Formula III, L_4 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or $-C(O)-$; R^{81} is hydrogen, fluoro, chloro, -CN, methyl, or methoxy, preferably hydrogen, chloro, -CN, or methyl; R^{82} is hydrogen; R^{83} is  , wherein R^{92}, R^{93}, R^{94}, R^{95}, and R^{96} are independently hydrogen, fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy or trifluoromethoxy, preferably hydrogen, chloro, methyl, trifluoromethyl, methoxy, ethoxy, or trifluoromethoxy, provided, however, that when R^{94} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy or trifluoromethoxy, at least one of R^{92}, R^{93}, R^{95}, and R^{96} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy or trifluoromethoxy.

[0045] In one embodiment of compounds of Formula III, L_4 is $-CH_2-$; R^{81} is fluoro, chloro, -CN, methyl, or methoxy, preferably chloro, -CN, or methyl; R^{82} is hydrogen; R^{83} is , wherein R^{94} is hydrogen and R^{92}, R^{93}, R^{95}, and R^{96} are independently hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy or trifluoromethoxy.

[0046] In one embodiment of compounds of Formula III, L_4 is $-CH_2-$, $-CH_2CH_2-$, -C(O)-, or $-CH(CH_3)-$, preferably $-CH_2-$ or -C(O)-; R^{81} is hydrogen or flouro; R^{82} is hydrogen; R^{83} is , wherein R^{92} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, chloro, methyl, or trifluoromethyl, and R^{93}, R^{94}, R^{95}, and R^{96} are independently hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy or trifluoromethoxy, preferably hydrogen or fluoro. In one embodiment, L_4 is $-CH_2-$, -C(O)-, or $-CH(CH_3)-$; R^{81} is hydrogen; R^{82} is hydrogen; R^{92} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, methyl, or trifluoromethyl; and R^{93}, R^{94}, R^{95}, and R^{96} are hydrogen. In one embodiment, L_4 is $-CH_2-$, -C(O)-, or $-CH(CH_3)-$; R^{81} is hydrogen; R^{82} is hydrogen; R^{92} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, methyl, or trifluoromethyl; R^{94}, R^{95}, and R^{96} are hydrogen; and R^{93} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, chloro, trifluoromethyl or methoxy, more preferably fluoro. In one embodiment, L_4 is $-CH_2-$, -C(O)-, or $-CH(CH_3)-$; R^{81} is hydrogen; R^{82} is hydrogen; R^{92} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, methyl, or trifluoromethyl; R^{93}, R^{95}, and R^{96} are hydrogen; and R^{94} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, chloro, methyl or trifluoromethyl, more preferably fluoro. In one embodiment, L_4 is $-CH_2CH_2-$ or -C(O)-; R^{81} is hydrogen; R^{82} is hydrogen; R^{92}, R^{95}, and R^{96} are hydrogen; R^{93} is hydrogen, fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, or trifluoromethoxy, more preferably fluoro, chloro, trifluoromethyl or methoxy; and R^{94} is hydrogen, fluoro, or chloro; provided, however, that when L_4 is -C(O)- and R^{94} is fluoro or chloro, R^{93} is not hydrogen. In one

embodiment, L_4 is $-CH_2CH_2-$; R^{81} is hydrogen; R^{82} is hydrogen; R^{92}, R^{94}, R^{95}, and R^{96} are hydrogen; and R^{93} is hydrogen, fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably hydrogen or fluoro. In one embodiment, L_4 is -C(O)-; R^{81} is hydrogen; R^{82} is hydrogen; R^{92}, R^{95}, and R^{96} are hydrogen; R^{93} is fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, difluoromethoxy, or trifluoromethoxy, preferably fluoro, chloro, trifluoromethyl or methoxy; and R^{94} is hydrogen, fluoro, or chloro.

[0047] In one embodiment of compounds of Formula III, R^{83} is pyrrolidine, morpholine, pyridine, pyrimidine, pyrazine, pyrazole, isoxazole, imidazol, or benzimidazole, wherein R^{83} is optionally substituted with one or more substituents independently selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, cycloalkylamino, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$, preferably wherein R^{83} is optionally substituted with 1 or 2 substituents independently selected from fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, or cycloalkylamino, more preferably fluoro, chloro, methyl, trifluoromethyl, methoxy or morpholine.

[0048] In one embodiment of compounds of Formula III, L_4 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or -C(O)-, preferably $-CH_2-$, $-CH_2CH_2-$, or -C(O)-; R^{81} is hydrogen, fluoro, chloro, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, or fluoro substituted lower alkoxy, preferably hydrogen, chloro, methyl or -CN; R^{82} is hydrogen; and R^{83} is pyrrolidine, morpholine, pyridine, pyrimidine, pyrazine, pyrazole, isoxazole, imidazole, or benzimidazole, wherein R^{83} is optionally substituted with 1 or 2 substituents independently selected from fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, or cycloalkylamino, preferably fluoro, chloro, methyl, trifluoromethyl, methoxy or morpholine.

[0049] In one embodiment of compounds of Formula III, the compound is selected from the group consisting of:
Pyridin-3-ylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0094)**,
(5-Methyl-isoxazol-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0095)**,
(2-Pyrrolidin-1-yl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0096)**,
[1-(4-Methanesulfonyl-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0097)**,
(2-Morpholin-4-yl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0099)**,
3,4-Dichloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide **(P-0100)**,
2-Chloro-4-fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide **(P-0101)**,
2,5-Dimethyl-2H-pyrazole-3-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-

yl]-amide (**P-0102**),

Thiophene-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0103**),

2-Methoxy-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0104**),

N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0105**),

Pyrazine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0106**),

Pyridine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0107**),

6-Methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-nicotinamide (**P-0108**),

4-Fluoro-3-methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0109**),

5-Methyl-pyrazine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0110**),

3-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0111**),

4-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethyl-benzamide (**P-0112**),

N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethoxy-benzamide (**P-0113**),

N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethyl-benzamide (**P-0114**),

3-Chloro-4-fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0115**),

3,4-Difluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0116**),

2-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0117**),

5-Fluoro-2-methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0118**),

2-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0119**),

3-Methoxy-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0120**),

3-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0121**),

3-Methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0122**),

2-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0123**),

((R)-1-Phenyl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0125**),

(3-Morpholin-4-yl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0126**),

[1-(2-Fluoro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0127**),

[2-(3-Fluoro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine

(P-0128),
(3-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0129),
(1-Methyl-1H-imidazol-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0130),
(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0131),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (P-0181),
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (P-0182),
(3-Chloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0183),
(2-Chloro-6-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0210),
Phenethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0211),
(2,4-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0212),
(2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0213),
(3-Bromo-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0214),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0215),
(2-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0216),
(2-Methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0217),
(1-Methyl-1H-benzoimidazol-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0218),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0219),
(1H-Benzoimidazol-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0220),
(2-Chloro-4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0221),
(5-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0222),
(3-Fluoro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0223),
(6-Methoxy-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine

(P-0224),
(4-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0225),
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (P-0226),
(3,5-Dichloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0227),
(6-Morpholin-4-yl-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0228),
(3-Fluoro-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0229),
(5-Fluoro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0230),
(3-Chloro-pyridin-4-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0235),
3-{6-[(3-Chloro-pyridin-4-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0256),
3-[6-(4-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0257),
Propane-1-sulfonic acid (2,4-difluoro-3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (P-0258),
Propane-1-sulfonic acid (3-{[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-2,4-difluoro-phenyl)-amide (P-0259),
3-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0269),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-benzyl)-amine (P-0270),
3-[6-(2-Fluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0271),
(2-Fluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0272),
3-{6-[(6-Trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0273),
3-[6-(2-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0274),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-

amine **(P-0275)**,
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine **(P-0276)**,
3-[6-(2,6-Difluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0277)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-difluoro-benzyl)-amine **(P-0278)**,
(2-Chloro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0279)**,
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0280)**,
3-[6-(2-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0281)**,
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0282)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **(P-0283)**,
3-{6-[(6-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0284)**,
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0285)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine **(P-0286)**,
3-{6-[(2-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0287)**,
(2-Ethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0288)**,
(2,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0296)**,
(2,5-Difluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0297)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,5-difluoro-benzyl)-amine **(P-0298)**,
3-[6-(2,5-Difluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0299)**,
3-[6-(2-Trifluoromethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **(P-0321)**,
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethoxy-benzyl)-amine

(P-0322),
3-[6-(2-Ethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0323),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (P-0324),
[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (P-0325),
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (P-0326),
(2-Chloro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0327),
(2-Chloro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0328),
(2,5-Difluoro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0329),
(2,5-Difluoro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0330),
[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (P-0331),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0332),
(2,6-Difluoro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0333),
(2,6-Difluoro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0334),
(2-Methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0336),
3-[6-(2-Methoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0337),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-difluoromethoxy-benzyl)-amine (P-0338),
3-[6-(2-Difluoromethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0339),
(2,6-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0340),
(2,6-Difluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0341),
(2,4-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0342),

(3-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0343**),
(2-Fluoro-4-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0344**),
(4-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0345**),
(3-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0346**),
(2-Morpholin-4-yl-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0347**),
(4-Chloro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0348**),
(2-Chloro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0349**),
(2-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0350**),
(2,3-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0351**),
(2-Fluoro-3-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0352**),
Dimethyl-(5-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-amine (**P-0353**),
(3-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0354**),
(5-Fluoro-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0355**),
(3,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0356**),
(2-Propoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0357**),
(2-Morpholin-4-yl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0358**),
(2-Chloro-3-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0359**),
(2-Fluoro-6-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0360**),
[2-(2-Morpholin-4-yl-ethoxy)-benzyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0361**),
(2,3-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0362**),
(2-Chloro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-

amine (**P-0363**),
(2-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0364**),
(2-Fluoro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0365**),
(5-Fluoro-2-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0366**),
(2-Difluoromethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0367**),
(2-Fluoro-4-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0368**),
[2-(3-Dimethylamino-propoxy)-benzyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0369**),
(2,6-Dimethoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0370**),
(2-Fluoro-5-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0371**),
(4-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0372**),
(3-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0373**),
(6-Cyclopentyloxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0374**),
(5-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0375**),
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[2-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine (**P-0376**),
Propane-1-sulfonic acid (2-fluoro-3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-0377**),
(2,5-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0380**),
Pyrimidin-5-ylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0381**),
(5-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0382**),
(2-Ethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0383**),
2,2-Dimethyl-N-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-propionamide (**P-0384**),

Methyl-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-amine **(P-0385)**,
Methyl-(5-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-amine **(P-0386)**,
(2-Chloro-4-methanesulfonyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0387)**,
Possibly to be added (P-0388),
(5-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0397)**,
Dimethyl-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-amine **(P-0399)**,
(5-Chloro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0400)**,
(2-Methoxy-pyrimidin-5-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0401)**,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine **(P-0409)**,
1-(3-Fluoro-phenyl)-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-urea **(P-0412)** , and all salts, prodrugs, tautomers, and isomers thereof.

[0050] In one embodiment, a compound of the invention is:
(4-Chloro-benzyl)-[6-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridazin-3-yl]-amine **(P-0092)**,
(4-Morpholin-4-ylmethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0093)**,
(2-Methoxy-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0098)**,
[4-Chloro-1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-[1-(4-fluoro-phenyl)-meth-(E)-ylidene]-amine **(P-0166)**,
((2,2-Difluoro-benzo[1,3]dioxol-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **(P-0398)**; or
any salts, prodrugs, tautomers, and isomers thereof.

[0051] In certain embodiments of the above compounds, compounds are excluded where N (except where N is a heteroaryl ring atom), O, or S is bound to a carbon that is also bound to N (except where N is a heteroaryl ring atom), O, or S, except where the carbon forms a double bond with one of the heteroatoms, such as in an amide, carboxylic acid, and the like; or where N (except where N is a heteroaryl ring atom), O, C(S), C(O), or $S(O)_n$ (n is 0-2) is bound to an alkene carbon

of an alkenyl group or bound to an alkyne carbon of an alkynyl group; accordingly, in certain embodiments compounds which include linkages such as the following are excluded from the present invention: -NR-CH_2-NR-, -O-CH_2-NR-, -S-CH_2-NR-, -NR-CH_2-O-, –O-CH_2-O-, -S-CH_2-O-,–NR-CH_2-S-, –O-CH_2-S-, –S-CH_2-S-, -NR-CH=CH-, -CH=CH-NR-, -NR-C≡C-, -C≡C-NR-, -O-CH=CH-, -CH=CH-O-, -O-C≡C-, -C≡C-O-, -$S(O)_{0-2}$-CH=CH-, -CH=CH-$S(O)_{0-2}$-, –$S(O)_{0-2}$-C≡C-, -C≡C-$S(O)_{0-2}$-, –C(O)-CH=CH-, -CH=CH-C(O)-, -C≡C-C(O)-, or -C(O)-C≡C-, -C(S)-CH=CH-, -CH=CH-C(S)-, -C≡C-C(S)-, or -C(S)-C≡C-.

[0052] In reference to compounds herein, specification of a compound or group of compounds includes pharmaceutically acceptable salts of such compound(s), prodrug(s), and all stereoisomers, unless clearly indicated to the contrary. In reference to compounds of Formula II, it is understood that such reference includes compounds of Formulae IIa, IIb, IIe, IIg and IIp, and all sub-embodiments thereof.

[0053] In another aspect, the invention provides methods for treating a c-kit-mediated disease or condition in an animal subject (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal c-kit activity (e.g. kinase activity). Invention methods involve administering to the subject suffering from or at risk of a c-kit-mediated disease or condition an effective amount of a compound of Formula II or Formula III, and all sub-embodiments thereof. In one embodiment, the c-kit mediated disease is selected from the group consisting of malignancies, including, but not limited to, mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including, but not limited to, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia.

[0054] In a related aspect, compounds of Formula II or Formula III, and all sub-embodiments thereof, can be used in the preparation of a medicament for the treatment of a c-kit-mediated disease or condition selected from the group consisting of malignancies, including, but not limited to, mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic

leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including, but not limited to, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia.

[0055] In a further aspect, the invention provides methods for treating a c-fms-mediated disease or condition in an animal subject (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal c-fms activity (e.g. kinase activity). Invention methods involve administering to the subject suffering from or at risk of a c-fms-mediated disease or condition an effective amount of compound of Formula II or Formula III, and all sub-embodiments thereof. In one embodiment, the c-fms mediated disease is selected from the group consisting of immune disorders, including, but not limited to, rheumatoid arthritis, systemic lupus erythematosis (SLE), and transplant rejection; inflammatory diseases including, but not limited to, osteoarthritis, inflammatory bowel syndrome, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage activation syndrome), multicentric reticulohistiocytosis, and atherosclerosis; metabolic disorders, including, but not limited to, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, and lipolysis; disorders of bone structure, mineralization and bone formation and resorption, including, but not limited to, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), peri-prosthetic or wear-debris-mediated osteolysis, and metastasis of cancer to bone; kidney and genitourinary diseases, including, but not limited to, endometriosis, nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications (e.g. diabetic nephropathy), and renal hypertrophy; disorders of the central nervous system, including, but not limited to, multiple sclerosis, stroke, Alzheimer's disease and Parkinson's disease; inflammatory and chronic pain, including, but not limited to, bone pain; and cancers, including, but not limited to, multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), prostate cancer, breast cancer, ovarian cancer, melanoma, glioblastoma multiforme, metastasis of tumors to other tissues, and other chronic myeloproliferative diseases such as myelofibrosis.

[0056] In a related aspect, compounds of Formula II or Formula III, and all sub-embodiments thereof, can be used in the preparation of a medicament for the treatment of a c-fms-mediated disease or condition selected from the group consisting of immune disorders, including, but not limited to, rheumatoid arthritis, systemic lupus erythematosis (SLE), and transplant rejection;

inflammatory diseases including, but not limited to, osteoarthritis, inflammatory bowel syndrome, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage activation syndrome), multicentric reticulohistiocytosis, and atherosclerosis; metabolic disorders, including, but not limited to, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, and lipolysis; disorders of bone structure, mineralization and bone formation and resorption, including, but not limited to, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), peri-prosthetic or wear-debris-mediated osteolysis, and metastasis of cancer to bone; kidney and genitourinary diseases, including, but not limited to, endometriosis, nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications (e.g. diabetic nephropathy), and renal hypertrophy; disorders of the central nervous system, including, but not limited to, multiple sclerosis, stroke, Alzheimer's disease and Parkinson's disease; inflammatory and chronic pain, including, but not limited to, bone pain; and cancers, including, but not limited to, multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), prostate cancer, breast cancer, ovarian cancer, melanoma, glioblastoma multiforme, metastasis of tumors to other tissues, and other chronic myeloproliferative diseases such as myelofibrosis.

[0057] In a further aspect, the invention provides methods for treating, in an animal subject (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), a disease or condition mediated by c-fms and c-kit, e.g., a disease or condition characterized by abnormal c-fms activity and c-kit activity (e.g. kinase activity). Invention methods involve administering to the subject suffering from or at risk of a disease or condition mediated by c-fms and c-kit an effective amount of compound of Formula II or Formula III, and all sub-embodiments thereof. In one embodiment, the condition mediated by c-fms and c-kit is selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, prostate cancer, canine mast cell tumors, metastasis of cancer to bone or other tissues, chronic myeloproliferative diseases such as myelofibrosis, renal hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, osteoarthritis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosis, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease, emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage

activation syndrome), multicentric reticulohistiocytosis, atherosclerosis, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), peri-prosthetic or wear-debris-mediated osteolysis, endometriosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, stroke, Alzheimer's disease, Parkinson's disease, inflammatory pain, chronic pain, and bone pain.

[0058] In a related aspect, compounds of Formula II or Formula III, and all sub-embodiments thereof, can be used in the preparation of a medicament for the treatment of a disease or condition mediated by c-fms and c-kit selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, prostate cancer, canine mast cell tumors, metastasis of cancer to bone or other tissues, chronic myeloproliferative diseases such as myelofibrosis, renal hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, osteoarthritis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosis, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease, emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage activation syndrome), multicentric reticulohistiocytosis, atherosclerosis, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g. osteomyelitis), peri-prosthetic or wear-debris-mediated osteolysis, endometriosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, stroke, Alzheimer's disease, Parkinson's disease, inflammatory pain, chronic pain, and bone pain.

[0059] In particular embodiments, the compound has an IC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, or less than 5 nM as determined in a generally accepted kinase activity assay. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-kit than on Ret, PDGF, or both Ret and PDGF. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-kit than on c-fms. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-fms than on c-kit. In certain embodiments, the

compound has in combination each pairing of activity (e.g. IC_{50}) and/or selectivity as specified in this paragraph.

[0060] In particular embodiments, the compound has an IC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, or less than 5 nM as determined in a generally accepted kinase activity assay for c-kit, c-fms, or both c-kit and c-fms kinase activity. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-kit, c-fms, or both c-kit and c-fms than on Ret, PDGF, or both Ret and PDGF.

[0061] In particular embodiments, the compound has an IC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, or less than 5 nM as determined in a generally accepted kinase activity assay for c-kit, c-fms, or both c-kit and c-fms kinase activity, and further has an IC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, or less than 5 nM as determined in a generally accepted kinase activity assay for at least one of HGK, TrkA, or TrkB kinase activity.

[0062] An additional aspect of this invention relates to compositions that include a therapeutically effective amount of a compound of Formula II or Formula III and all sub-embodiments thereof and at least one pharmaceutically acceptable carrier, excipient, and/or diluent, including combinations of any two or more compounds of Formula II or Formula III. The composition can further include one or more different pharmacologically active compounds, which can include one or more compounds of Formula II or Formula III.

[0063] In one aspect, the invention provides a method of treating a cancer by administering to the subject an effective amount of a composition including a compound of Formula II or Formula III, in combination with one or more other therapies or medical procedures effective in treating the cancer. Other therapies or medical procedures include suitable anticancer therapy (e.g. drug therapy, vaccine therapy, gene therapy, photodynamic therapy) or medical procedure (e.g. surgery, radiation treatment, hyperthermia heating, bone marrow or stem cell transplant). In one aspect, the one or more suitable anticancer therapies or medical procedures is selected from treatment with a chemotherapeutic agent (e.g. chemotherapeutic drug), radiation treatment (e.g. x-ray, γ-ray, or electron, proton, neutron, or α particle beam), hyperthermia heating (e.g. microwave, ultrasound, radiofrequency ablation), Vaccine therapy (e.g. AFP gene hepatocellular carcinoma vaccine, AFP adenoviral vector vaccine, AG-858, allogeneic GM-CSF-secretion breast cancer vaccine, dendritic cell peptide vaccines), gene therapy (e.g. Ad5CMV-p53 vector, adenovector encoding MDA7,

adenovirus 5-tumor necrosis factor alpha), photodynamic therapy (e.g. aminolevulinic acid, motexafin lutetium), surgery, and bone marrow and stem cell transplantation.

[0064] In one aspect, the invention provides a method of treating a cancer by administering to the subject an effective amount of a composition including a compound of Formula II or Formula III, in combination with one or more suitable chemotherapeutic agents. In one aspect, the one or more suitable chemotherapeutic agents is selected from an alkylating agent, including, but not limited to, adozelesin, altretamine, bizelesin, busulfan, carboplatin, carboquone, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mechlorethamine, melphalan, oxaliplatin, piposulfan, semustine, streptozocin, temozolomide, thiotepa, and treosulfan; an antibiotic, including, but not limited to, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, menogaril, mitomycin, mitoxantrone, neocarzinostatin, pentostatin, and plicamycin; an antimetabolite, including, but not limited to, azacitidine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, ftorafur, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, raltitrexed, thioguanine, and trimetrexate; an immunotherapy, including, but not limited to, alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, and 90 Y ibritumomab tiuxetan; a hormone or hormone antagonist, including, but not limited to, anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene; a taxane, including, but not limited to, DJ-927, docetaxel, TPI 287, paclitaxel and DHA-paclitaxel; a retinoid, including, but not limited to, alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; an alkaloid, including, but not limited to, etoposide, homoharringtonine, teniposide, vinblastine, vincristine, vindesine, and vinorelbine; an antiangiogenic agent, including, but not limited to, AE-941 (GW786034, Neovastat), ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide; a topoisomerase inhibitor, including, but not limited to, amsacrine, edotecarin, exatecan, irinotecan (also active metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin)), rubitecan, topotecan, and 9-aminocamptothecin; a kinase inhibitor, including, but not limited to, erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, sorafenib, sunitinib malate, AEE-788, AG-013736, AMG 706, AMN107, BMS-354825, BMS-599626, UCN-01 (7-hydroxystaurosporine), and vatalanib; a targeted signal transduction inhibitor including, but not limited to bortezomib, geldanamycin, and rapamycin; a biological response modifier, including, but not limited to, imiquimod, interferon-α, and interleukin-2; and other chemotherapeutics, including, but not limited to 3-AP (3-amino-2-carboxyaldehyde thiosemicarbazone), aminoglutethimide, asparaginase, bryostatin-1, cilengitide, E7389, ixabepilone, procarbazine, sulindac, temsirolimus,

tipifarnib. Preferably, the method of treating a cancer involves administering to the subject an effective amount of a composition of Formula II, Formula III or Formula IV in combination with a chemotherapeutic agent selected from 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, vinblastine, bevacizumab, cetuximab, or erlotinib.

[0065] In another aspect, the invention provides a method of treating or prophylaxis of a disease or condition in a mammal, by administering to the mammal a therapeutically effective amount of a compound of Formula II or Formula III, a prodrug of such compound, or a pharmaceutically acceptable salt of such compound or prodrug. The compound can be alone or can be part of a composition.

[0066] In a related aspect, the invention provides kits that include a composition as described herein. In particular embodiments, the composition is packaged, e.g., in a vial, bottle, flask, which may be further packaged, e.g., within a box, envelope, or bag; the composition is approved by the U.S. Food and Drug Administration or similar regulatory agency for administration to a mammal, e.g., a human; the composition is approved for administration to a mammal, e.g., a human, for a c-kit- and/or c-fms-mediated disease or condition; the kit of the invention includes written instructions on use and/or other indication that the composition is suitable or approved for administration to a mammal, e.g., a human, for a c-kit- and/or c-fms-mediated disease or condition; the composition is packaged in unit dose or single dose form, e.g., single dose pills, capsules, or the like.

[0067] In another aspect, the present invention also provides a method for modulating c-kit or c-fms activity by contacting c-kit or c-fms with an effective amount of a compound of Formula II or Formula III and all sub-embodiments thereof active on c-kit and/or c-fms (such as compounds developed using methods described herein). The compound is preferably provided at a level sufficient to modulate the activity of the c-kit or c-fms by at least 10%, more preferably at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater than 90%. In many embodiments, the compound will be at a concentration of about 1 μM, 100 μM, or 1 mM, or in a range of 1-100 nM, 100-500 nM, 500-1000 nM, 1-100 μM, 100-500 μM, or 500-1000 μM. In particular embodiments, the contacting is carried out *in vitro*.

[0068] Additional aspects and embodiments will be apparent from the following Detailed Description and from the claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0069] As used herein the following definitions apply:

[0070] "Halo" and "halogen" refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0071] "Hydroxyl" and "hydroxy" refer to the group -OH.

[0072] "Thiol" refers to the group -SH.

[0073] "Lower alkyl" alone or in combination means an alkane-derived radical containing from 1 to 6 carbon atoms (unless specifically defined) that includes a straight chain alkyl or branched alkyl. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. In many embodiments, a lower alkyl is a straight or branched alkyl group containing from 1-6, 1-4, or 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. "Optionally substituted lower alkyl" denotes lower alkyl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkyl" denotes a lower alkyl group substituted with one or more fluoro atoms, such as perfluoroalkyl, where preferably the lower alkyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions are attached at any available atom to produce a stable compound, when optionally substituted alkyl is an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the alkyl R group is such that substitution of the alkyl carbon bound to any -O-, -S-, or -N- of the moiety (except where -N- is a heteroaryl ring atom) excludes substituents that would result in any -O-, -S-, or -N- of the substituent (except where -N- is a heteroaryl ring atom) being bound to the alkyl carbon bound to any -O-, -S-, or -N- of the moiety.

[0074] "Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-10, also 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, and the like. A "substituted cycloalkyl" is a cycloalkyl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0075] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally fused with benzo or heteroaryl of 5-6 ring members.

Heterocycloalkyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. Heterocycloalkyl is also intended to include compounds in which one of the ring carbons is oxo substituted, i.e. the ring carbon is a carbonyl group, such as lactones and lactams. The point of attachment of the heterocycloalkyl ring is at a carbon or nitrogen atom such that a stable ring is retained. Examples of heterocycloalkyl groups include, but are not limited to, morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, pyrrolidonyl, piperazinyl, dihydrobenzofuryl, and dihydroindolyl. A "substituted heterocycloalkyl" is a heterocycloalkyl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0076] "Aryl" alone or in combination refers to a monocyclic or bicyclic ring system containing aromatic hydrocarbons such as phenyl or naphthyl, which may be optionally fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members. A "substituted aryl" is an aryl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0077] "Heteroaryl" alone or in combination refers to a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, quinaoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, and indolyl. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any heteroatoms are N. A "substituted heteroaryl" is a heteroaryl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0078] "Lower alkoxy" denotes the group $-OR^z$, where R^z is lower alkyl. "Substituted lower alkoxy" denotes lower alkoxy in which R^z is lower alkyl substituted with one or more substituents as indicated herein attached at any available atom to produce a stable compound. Preferably, substitution of lower alkoxy is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkoxy" denotes lower alkoxy in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkoxy is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions on

alkoxy are attached at any available atom to produce a stable compound, substitution of alkoxy is such that -O-, -S-, or –N- (except where N is a heteroaryl ring atom), are not bound to the alkyl carbon bound to the alkoxy -O-. Further, where alkoxy is described as a substituent of another moiety, the alkoxy oxygen is not bound to a carbon atom that is bound to an –O-, -S-, or –N- of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0079] "Lower alkylthio" denotes the group $-SR^{aa}$, where R^{aa} is lower alkyl. "Substituted lower alkylthio" denotes lower alkylthio in which R^{aa} is lower alkyl substituted with one or more substituents as indicated herein attached at any available atom to produce a stable compound. Preferably, substitution of lower alkylthio is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkylthio" denotes lower alkylthio in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkylthio is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions on alkylthio are attached at any available atom to produce a stable compound, substitution of alkylthio is such that -O-, -S-, or –N- (except where N is a heteroaryl ring atom), are not bound to the alkyl carbon bound to the alkylthio -S-. Further, where alkylthio is described as a substituent of another moiety, the alkylthio sulfur is not bound to a carbon atom that is bound to an –O-, -S-, or –N- of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0080] "Mono-alkylamino" denotes the group $-NHR^{bb}$ where R^{bb} is lower alkyl. "Di-alkylamino" denotes the group $-NR^{bb}R^{cc}$, where R^{bb} and R^{cc} are independently lower alkyl. "Cycloalkylamino" denotes the group $-NR^{dd}R^{ee}$, where R^{dd} and R^{ee} combine with the nitrogen to form a 5-7 membered heterocycloalkyl, where the heterocycloalkyl may contain an additional heteroatom within the ring, such as –O-, -N-, or –S-, and may also be further substituted with lower alkyl. Examples of 5-7 membered heterocycloalkyl include, but are not limited to, piperidine, piperazine, 4-methylpiperazine, morpholine, and thiomorpholine. While it is understood that when mono-alkylamino, di-alkylamino, or cycloalkylamino are substituents on other moieties that are attached at any available atom to produce a stable compound, the nitrogen of mono-alkylamino, di-alkylamino, or cycloalkylamino as substituents is not bound to a carbon atom that is bound to an –O-, -S-, or –N- of the other moiety.

[0081] As used herein, the term c-kit-mediated disease or condition refers to a disease or condition in which the biological function of c-kit affects the development and/or course of the disease or condition, and/or in which modulation of c-kit alters the development, course, and/or symptoms. For example, mutations in the c-kit gene such as the W42, Wv, and W41 mutations

reported by Herbst et al al (J. Biol. Chem., 1992, 267: 13210-13216) confer severe, intermediate, and mild phenotypic characteristics, respectively. These mutations attenuate the intrinsic tyrosine kinase activity of the receptor to different degrees and are models for the effect of modulation of c-kit activity. A c-kit mediated disease or condition includes a disease or condition for which c-kit inhibition provides a therapeutic benefit, e.g. wherein treatment with c-kit inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0082] As used herein, the term c-fms-mediated disease or condition refers to a disease or condition in which the biological function of c-fms affects the development and/or course of the disease or condition, and/or in which modulation of c-fms alters the development, course, and/or symptoms. For example, the *Csf1r*$^{-}$/*Csf1r*$^{-}$ mutant mouse of Dai et al (Blood, 2002, 99: 111-120) which lacks c-fms is an animal model for diseases or conditions wherein c-fms activity has been abolished. A c-fms mediated disease or condition includes a disease or condition for which c-fms inhibition provides a therapeutic benefit, e.g. wherein treatment with c-fms inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0083] As used herein, the term "composition" refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes that contains at least one pharmaceutically active compound and at least one pharmaceutically acceptable carrier or excipient.

[0084] The term "pharmaceutically acceptable" indicates that the indicated material does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration. For example, it is commonly required that such a material be essentially sterile, e.g., for injectibles.

[0085] In the present context, the terms "therapeutically effective" and "effective amount" indicate that the materials or amount of material is effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or medical condition, and/or to prolong the survival of the subject being treated.

[0086] As used herein, the term "modulating" or "modulate" refers to an effect of altering a biological activity, especially a biological activity associated with a particular biomolecule such as c-kit or c-fms. For example, an agonist or antagonist of a particular biomolecule modulates the activity of that biomolecule, *e.g.*, an enzyme.

[0087] The term "c-kit activity" refers to a biological activity of c-kit, particularly including kinase activity. The term "c-fms activity" refers to a biological activity of c-fms, particularly including kinase activity.

I. General

[0088] In one aspect, the present invention concerns compounds of Formula II, IIa, IIb, IIe, IIg, IIp or III and all sub-embodiments thereof, that are inhibitors of c-kit, c-fms, or both c-kit and c-fms, and the use of the compounds in treating diseases that are mediated by c-kit, c-fms, or both c-kit and c-fms.

Exemplary Diseases Associated with c-Kit.

[0089] The compounds described herein are useful for treating disorders related to c-kit e.g., diseases related to unregulated kinase signal transduction, including cell proliferative disorders, fibrotic disorders and metabolic disorders, among others. As described in more detail below and in Lipson et al., U.S. 20040002534 (U.S. application 10/600, 868, filed June 23, 2003) which is incorporated herein by reference in its entirety, cell proliferative disorders which can be treated by the present invention include cancers, and mast cell proliferative disorders.

[0090] The presence of c-kit has also been associated with a number of different types of cancers. In addition, the association between abnormalities in c-kit and disease are not restricted to cancer. As such, c-kit has been associated with malignancies, including mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia.

Exemplary diseases associated with c-fms

[0091] The presence of c-fms has been associated with a number of different types of diseases. As such, c-fms has been associated with immune disorders, including, but not limited to, rheumatoid arthritis, systemic lupus erythematosis (SLE), and transplant rejection; inflammatory diseases including, but not limited to, inflammatory bowel syndrome, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), emphysema, Kawasaki's Disease, hemophagocytic syndrome (macrophage activation syndrome), multicentric reticulohistiocytosis,

and atherosclerosis; metabolic disorders, including, but not limited to, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, obesity, and lipolysis; disorders of bone structure, mineralization and bone formation and resorption, including, but not limited to, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, infection-mediated osteolysis (e.g., osteomyelitis), peri-prosthetic or wear-debris-mediated osteolysis, and metastasis of cancer to bone; kidney and genitourinary diseases, including, but not limited to, endometriosis, nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications (e.g. diapetic nephropathy), and renal hypertrophy; disorders of the central nervous system, including, but not limited to, multiple sclerosis, stroke, Alzheimer's disease and Parkinson's disease; inflammatory and chronic pain, including, but not limited to, bone pain; and cancers, including, but not limited to, multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), prostate cancer, breast cancer, ovarian cancer, melanoma, glioblastoma multiforme, metastasis of tumors to other tissues, and other chronic myeloproliferative diseases such as myelofibrosis.

Exemplary diseases associated with TrkA and TrkB

[0092] **TrkA:** Target kinase TrkA (i.e., neurotrophic tyrosine kinase, receptor, type 1) is a 140 kDa tyrosine kinase encoded by chromosome 1q21-q22 (symbol: NTRK1). TrkA inhibitors may be useful in treating pain (e.g. chronic pain, neuropathic pain), cancer (e.g. prostate cancer, lung cancer, myeloid leukemia, pancreatic cancer), arthritis, allergic disorders (e.g. asthma), diabetic retinopathy, macular degeneration and psoriasis.

[0093] **TrkB:** Target kinase TrkB (i.e., neurotrophic tyrosine kinase, receptor, type 2) is a 145 kDa tyrosine kinase encoded by chromosome 9q22.1 (symbol: NTRK2). TrkB inhibitors may be useful in treating various cancers and their metastases (e.g. prostate cancer, lung cancer, Wilm's tumors, neuroblastoma, and pancreatic cancer), and various neuropathies (e.g. stroke, multiple sclerosis, transverse myelitis, and encephalitis).

Exemplary diseases associated with HGK

[0094] **HGK:** Target kinase HGK (i.e., Hematopoietic progenitor kinase/Germinal center kinase-like Kinase, aka mitogen-activated protein kinase kinase kinase kinase 4) is a 130 kDa serine/threonine kinase encoded by chromosome 2q11.2-q12 (symbol: MAP4K4). HGK inhibitors may be useful in treating metabolic indications, including re-sensitizing fat and muscle cells to insulin, ameliorating the pathology in adipocytes, ameliorating the pathology in muscle cells, and

type II diabetes; a broad range of oncology indications, including blocking the migration, invasion and metastasis in many different tumor types; and T-cell mediated autoimmune diseases.

V. Organic Synthetic Techniques

[0095] A wide array of organic synthetic techniques exist in the art to meet the challenge of constructing potential modulators. Many of these organic synthetic methods are described in detail in standard reference sources utilized by those skilled in the art. One example of suh a reference is March, 1994, Advanced Organic Chemistry; Reactions, Mechanisms and Structure, New York, McGraw Hill. Thus, the techniques useful to synthesize a potential modulator of kinase function are readily available to those skilled in the art of organic chemical synthesis.

VI. Alternative Compound Forms or Derivatives

[0096] Alternative forms or derivatives, such as (a) Isomers, Prodrugs, and Active Metabolites (b) Tautomers, Stereoisomers, Regioisomers, and Solvated Forms (c) Prodrugs and Metabolites (d) Pharmaceutically acceptable salts and (e) Polymorphic forms, are described, for example, in US Patent Application Publication number US 2007/0032519, the disclosure of which is hereby incorporated by reference in its entirety.

VII. Administration

[0097] The methods and compounds will typically be used in therapy for human subjects. However, they may also be used to treat similar or identical indications in other animal subjects. In this context, the terms "subject," "animal subject," and the like refer to human and non-human vertebrates, e.g. mammals, such as non-human primates, sports and commercial animals, e.g., equines, bovines, porcines, ovines, rodents, and pets, e.g., canines and felines. A description of possible methods and routes of administration may be found, for example, in US Patent Application Publication number US 2007/0032519, the disclosure of which is hereby incorporated by reference in its entirety.

EXAMPLES

[0098] A number of examples illustrative of the present invention are described below. In most cases, alternative techniques could also be used. The examples are intended to be illustrative and are not limiting or restrictive to the scope of the invention. Unless specifically noted to the contrary, in cases where a compound number is not preceeded by a "P-" (e.g., "P-0001") in the Examples section, compound naming and/or enumeration is not related to naming and/or enumeration employed in other sections of this application. Similarly, structure and substituent

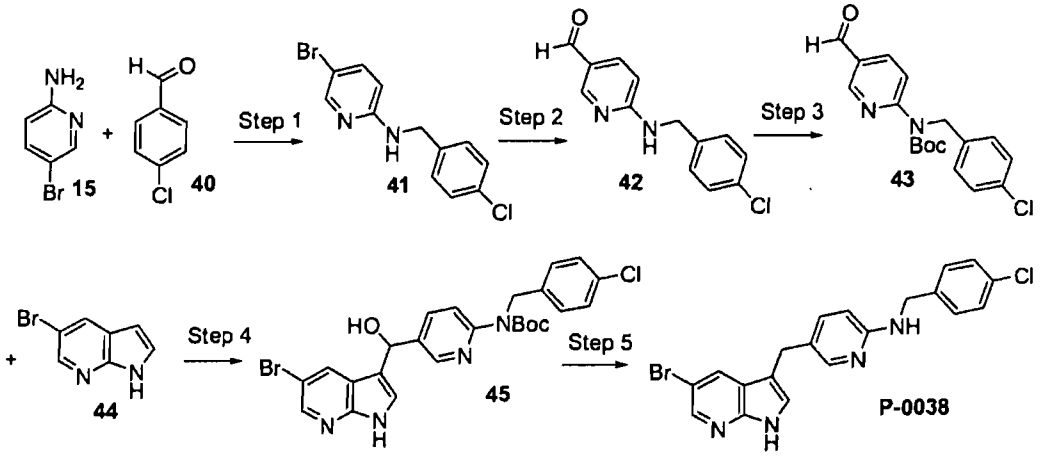
naming and enumeration within the Examples are independent of structure and substituent naming and enumeration in above sections of this application unless clearly indicated otherwise.

[0099] In the following Examples, it is understood that the solvents and reagents used or suggested are not limiting, and can be substituted appropriately with solvents and reagents known to those of skill in the art. Reaction products may be isolated by means known in the art, such as extraction with a suitable solvent, precipitation from a suitable solvent, chromatography using a suitable solvent system, including silica gel column chromatography, HPLC, preparative TLC, and the like. Exemplary methods for synthesis of compounds of the present invention may be found in US Patent Application Publication number US 2007/0032519, the disclosure of which is hereby incorporated by reference. The 1H-pyrrolo[2,3-b]pyridine core of compounds described in the examples may also be referred to as 7-azaindole in the examples.

Example 1: Synthesis of [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine (P-0038)

[0100] [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine **P-0038** was synthesized in 5 steps from commercially available 2-Amino-5-bromopyridine **15** as shown in Scheme 19.

Scheme 19



Step 1- Synthesis of (5-Bromo-pyridin-2-yl)-(4-chloro-benzyl)-amine (**41**)

[0101] To 2-Amino-5-bromopyridine (**15**, 6.10 g, 0.0352 mol) in toluene (90.0 mL) were added 4-chlorobenzaldehyde (**40**, 5.00 g, 0.0356 mol), trifluoroacetic acid (8.0 mL, 0.10 mol) and triethylsilane (16.5 mL, 0.103 mol). The reaction was heated to reflux for 48 hours. The reaction

was concentrated, poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude residue was crystallized with ethyl acetate to give compound (**41**, 6.8 g, 65.4%).

Step 2 – Synthesis of 6-(4-Chloro-benzylamino)-pyridine-3-carbaldehyde (**42**)

[0102] To (5-Bromo-pyridin-2-yl)-(4-chloro-benzyl)-amine (**41**, 10.00 g, 0.03360 mol) in tetrahydrofuran (400.0 mL) under an atmosphere of nitrogen at -78 °C was added n-butyllithium (17.5 mL, 2.00 M in cyclohexane). After 90 minutes, tert-butyllithium (42.00 mL, 1.70 M in hexane) was added to the reaction. After 80 minutes, N,N-dimethylformamide (6.9 mL, 0.089 mol) was added to the reaction. The reaction mixture was stirred at -78 °C for 2 hours, then allowed to warm to room temperature for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to give the crude compound, which was crystallized from *tert*-butoxyl methyl ether to provide compound (**42**, 7.66 g, 92.2%).

Step 3 – Synthesis of (4-Chloro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**43**)

[0103] To 6-(4-Chloro-benzylamino)-pyridine-3-carbaldehyde (**42**, 2.00 g, 8.11 mmol) in dichloromethane (20.0 mL) were added triethylamine (1.70 mL, 12.2 mmol), di-tert-butyldicarbonate (2.00 g, 9.16 mmol) and 4-dimethylaminopyridine (52.3 mg, 0.43 mmol). The reaction was stirred at room temperature for 48 hours. The reaction was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give compound (**43**, 2.50 g, 89.3%).

Step 4 – Synthesis of {5-[(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl}-(4-chloro-benzyl)-carbamic acid tert-butyl ester (**45**)

[0104] To 5-bromo-7-azaindole (**44**, 198.0 mg, 1.01 mmol) in methanol (30.0 mL, 0.741 mol) were added (4-Chloro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**43**, 355.0 mg, 1.02 mmol) and potassium hydroxide (80.0 mg, 1.42 mmol). The reaction was stirred at room temperature 48 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 8% methanol in dichloromethane to give compound (**45**, 200.0 mg, 36.8%).

Step 5 – Synthesis of [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine (**P-0038**)

[0105] To {5-[(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl}-(4-chloro-benzyl)-carbamic acid tert-butyl ester (**45**, 180.0 mg, 0.33 mmol) in acetonitrile (30.0 mL) were added trifluoroacetic acid (2.0 mL, 0.026 mol) and triethylsilane (4.0 mL, 0.025 mol). The reaction was heated to reflux for 4 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 10% methanol in dichloromethane to give compound (**P-0038**, 120 mg, 85.2%). MS(ESI)$[M+H^+]^+$ = 427.2, 429.2.

[0106] Additional compounds were prepared following the protocol of Scheme 19, optionally replacing 4-chlorobenzaldehyde **40** with an appropriate aldehyde in Step 1 and optionally replacing 5-bromo-7-azaindole **44** with an appropriate azaindole in Step 4. The following compounds were made following this procedure:
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0181**),
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0182**),
3-[6-(4-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0257**),
3-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0269**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-benzyl)-amine (**P-0270**),
3-[6-(2-Fluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0271**),
(2-Fluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0272**),
3-{6-[(6-Trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0273**),
3-[6-(2-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0274**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0275**),
[5-(5-Methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-

amine (**P-0276**),
3-[6-(2,6-Difluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0277**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-difluoro-benzyl)-amine (**P-0278**),
(2-Chloro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0279**),
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0280**),
3-[6-(2-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0281**),
(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0282**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-0283**),
3-{6-[(6-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0284**),
(2-Methoxy-pyridin-3-ylmethyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0285**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-0286**),
3-{6-[(2-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0287**),
(2-Ethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0288**),
(2,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0296**),
(2,5-Difluoro-benzyl)-[5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0297**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,5-difluoro-benzyl)-amine (**P-0298**),
3-[6-(2,5-Difluoro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0299**),
3-[6-(2-Trifluoromethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0321**),
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethoxy-benzyl)-amine (**P-0322**),
3-[6-(2-Ethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile

(**P-0323**),

[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0325**),

[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0326**),

(2-Chloro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0327**),

(2-Chloro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0328**),

(2,5-Difluoro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0329**),

(2,5-Difluoro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0330**),

[5-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-0331**),

(6-Methoxy-pyridin-3-ylmethyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0332**),

(2,6-Difluoro-benzyl)-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0333**),

(2,6-Difluoro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0334**),

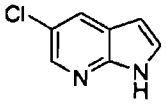
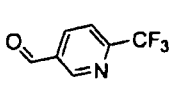
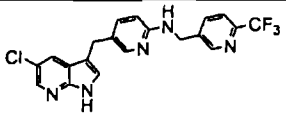
(2-Methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0336**),

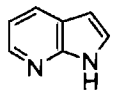
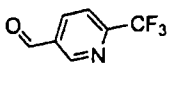
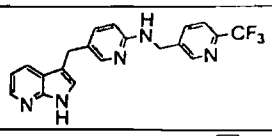
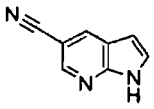
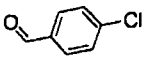
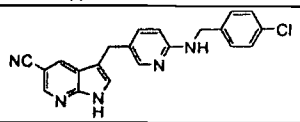
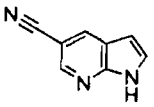
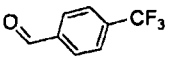
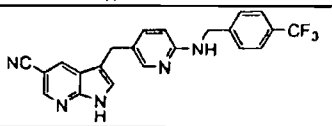
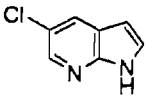
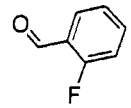
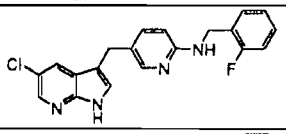
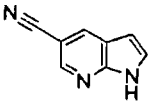
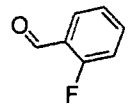
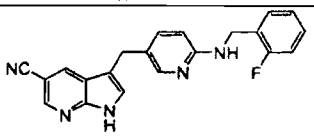
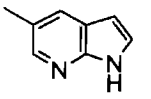
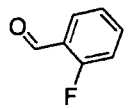
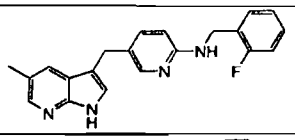
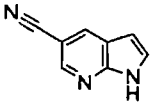
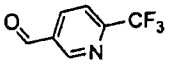
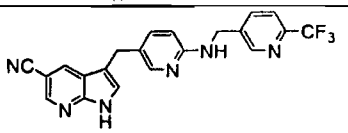
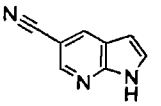
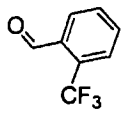
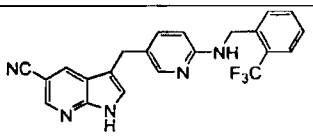
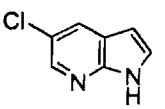
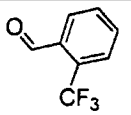
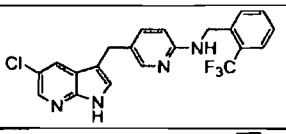
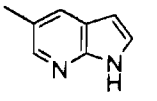
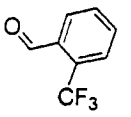
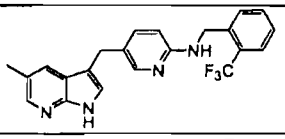
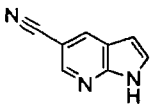
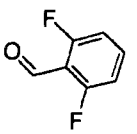
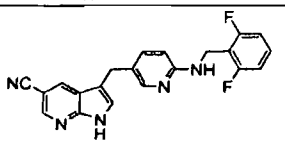
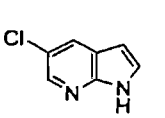
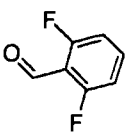
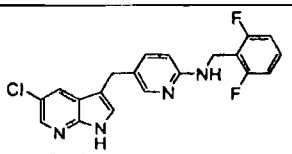
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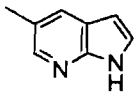
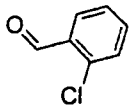
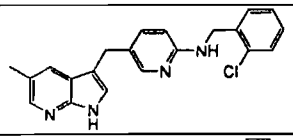
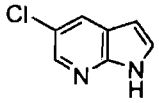
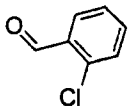
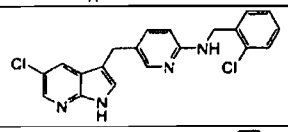
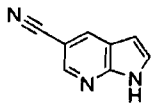
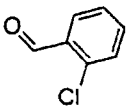
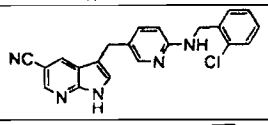
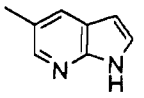
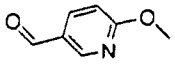
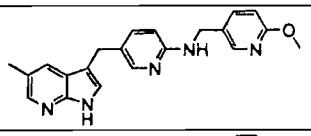
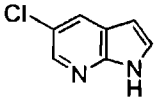
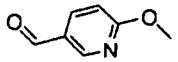
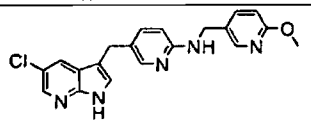
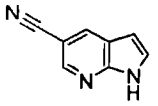
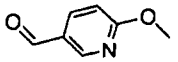
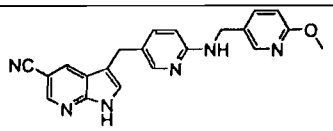
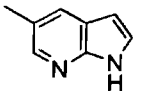
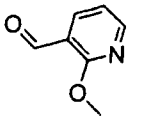
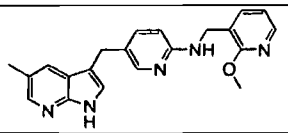
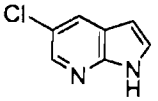
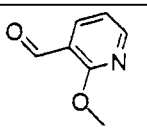
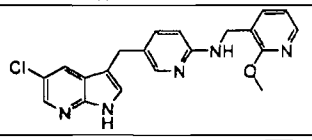
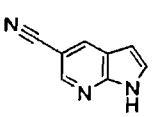
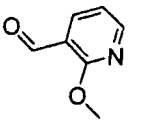
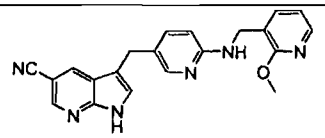
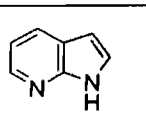
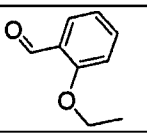
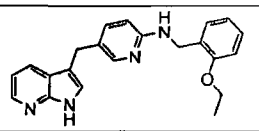
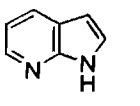
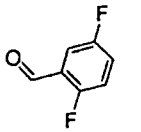
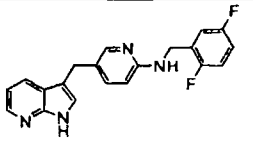
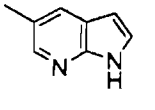
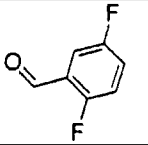
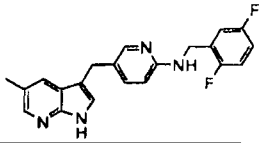
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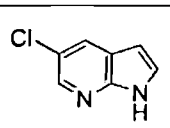
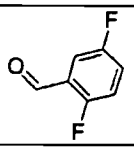
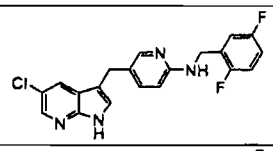
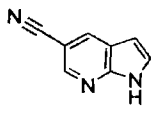
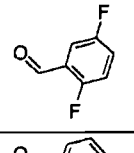
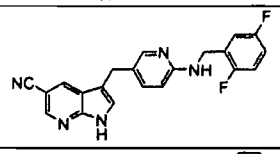
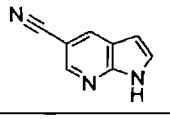
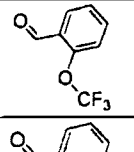
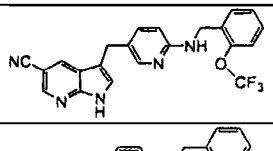
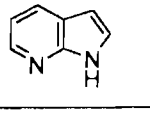
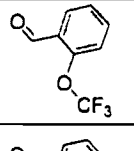
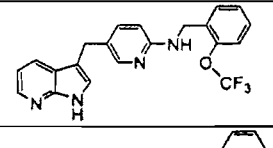
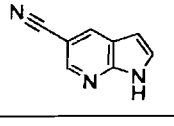
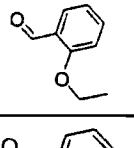
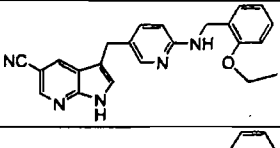
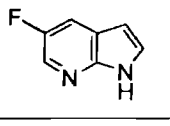
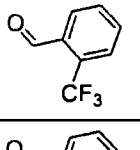
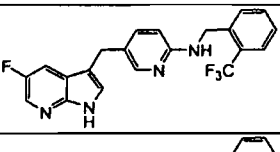
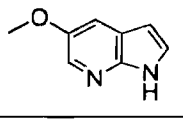
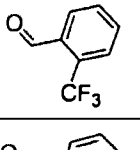
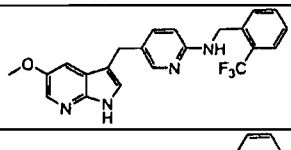
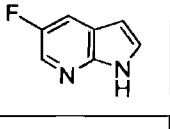
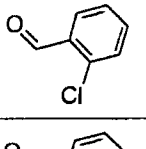
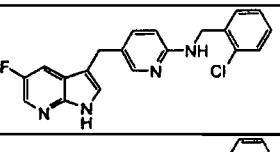
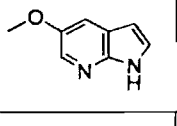
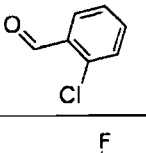
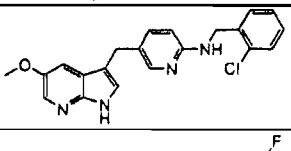
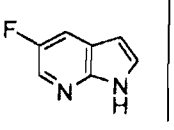
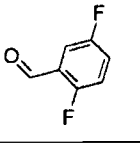
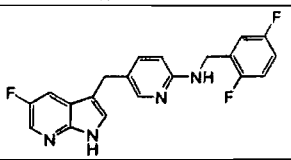
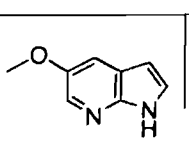
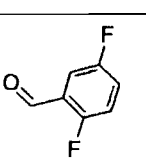
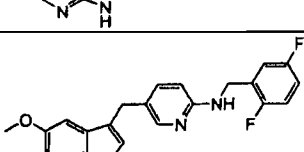
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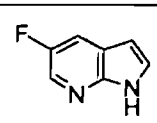
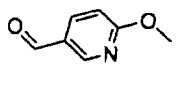
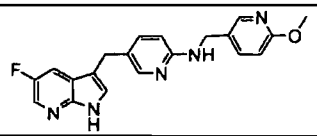
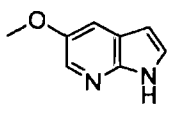
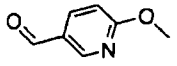
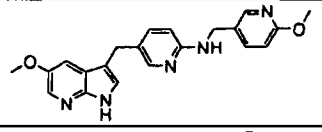
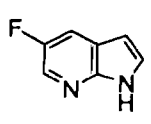
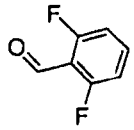
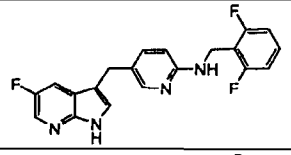
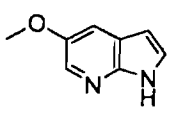
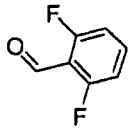
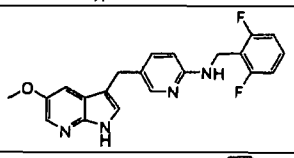
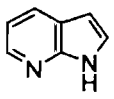
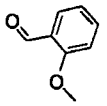
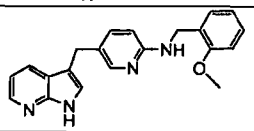
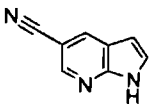
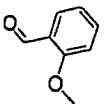
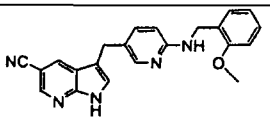
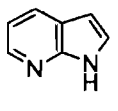
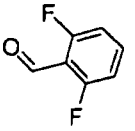
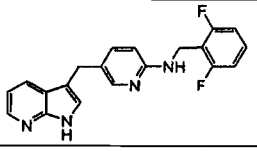
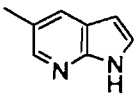
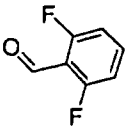
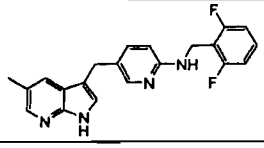
The following table indicates the aldehyde used in Step 1 in Column 3 and the azaindole used in Step 4 in Column 2 to provide the compound of Column 4. Column 1 provides the compound number and Column 5 the measured mass spectrometry result.

Compound number	Azaindole in Step 4	Aldehyde in Step 1	Compound structure	MS $[M+H^+]^+$
P-0181				418.2

P-0182				384.2
P-0257				374.2
P-0269				408.7
P-0270				367.0
P-0271				358.0
P-0272				347.0
P-0273				409.4
P-0274				408.5
P-0275				417.0
P-0276				397.6
P-0277				376.5
P-0278				385.0

P-0279				363.0
P-0280				383.3
P-0281				374.0
P-0282				360.8
P-0283				380.0
P-0284				371.5
P-0285				360.1
P-0286				380.0
P-0287				371.0
P-0288				359.6
P-0296				351.6
P-0297				365.5

P-0298				385.9
P-0299				376.4
P-0321				424.6
P-0322				399.5
P-0323				384.7
P-0325				401.5
P-0326				413.4
P-0327				367.2
P-0328				379.0
P-0329				369.7
P-0330				381.6

P-0331				364.5
P-0332				376.4
P-0333				369.6
P-0334				381.6
P-0336				345.7
P-0337				370.7
P-0340				351.5
P-0341				365.5

[0107] Additional compounds were prepared following the protocol of Scheme 19, Steps 4 and 5, replacing (4-Chloro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **43** with an appropriate protected aldehyde and 5-bromo-7-azaindole **44** with an appropriate azaindole in Step 4. Aldehydes were prepared as described in Example 60. The following compounds were made following this procedure:

3-{2-Chloro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0232**),

[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0233**),

[6-Chloro-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0234**),

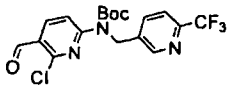
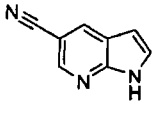
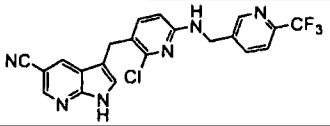
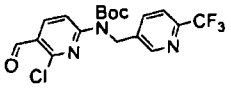
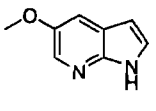
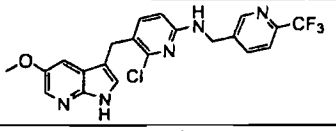
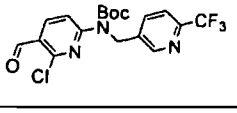
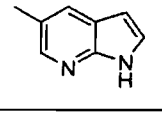
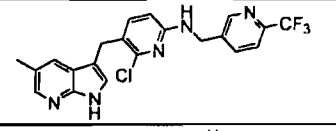
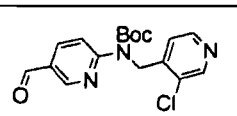
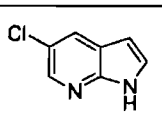
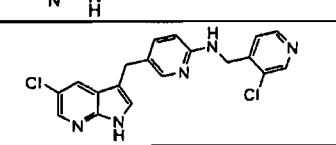
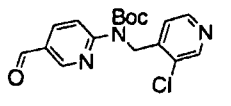
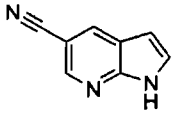
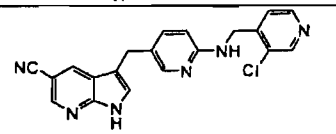
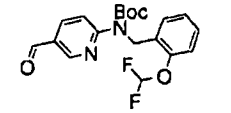
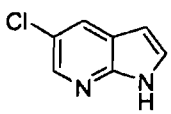
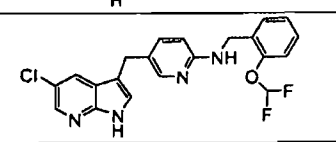
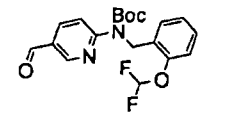
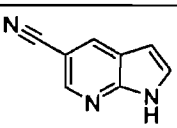
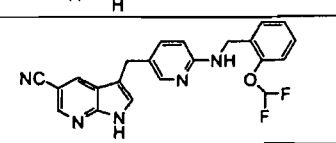
(3-Chloro-pyridin-4-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0235**),

3-{6-[(3-Chloro-pyridin-4-ylmethyl)-amino]-pyridin-3-ylmethyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0256**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-difluoromethoxy-benzyl)-amine (**P-0338**),

3-[6-(2-Difluoromethoxy-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**P-0339**),

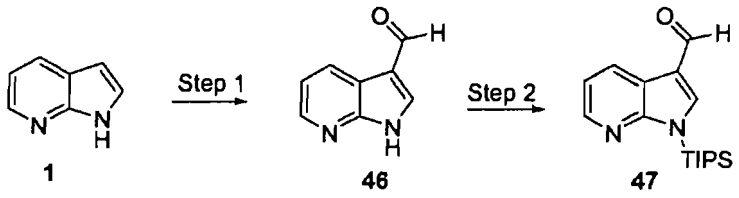
The following table indicates the aldehyde used in Column 2 and the azaindole used in Column 3 to provide the compound of Column 4. Column 1 provides the compound number and Column 5 the measured mass spectrometry result.

Compound number	Aldehyde	Azaindole	Compound	MS $[M+H^+]^+$
P-0232				443.0
P-0233				$[M-H^+]^-$ = 446.1
P-0234				430.1
P-0235				383.9
P-0256				375.2
P-0338				415.0
P-0339				406.6

Example 2: Synthesis of 1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde 47.

[0108] Compound **47** was synthesized in 2 steps from 7-azaindole **1** as described in Scheme 20.

Scheme 20



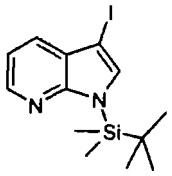
Step 1 – *Preparation of 1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde* (**46**):

[0109] To 1H-Pyrrolo[2,3-b]pyridine (**1**, 16.0 g, 135 mmol) in water (110 mL), were added hexamethylenetetramine (26.0 g, 185 mmol), and acetic acid (55.0 mL, 967 mmol). The reaction was refluxed for 12 hours. Water (329 mL) was added and the reaction was cooled to room temperature. The reaction was filtrated and washed with water to give compound (**46**, 15.0 g, 76%). MS(ESI)$[M+H^+]^+$ = 147.

Step 2 – *Preparation of 1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde* (**47**):

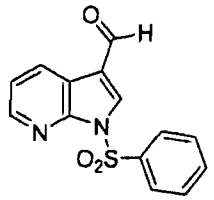
[0110] To 1H-Pyrrolo[2,3-b]pyridine-3-carbaldehyde (**46**, 4.05 g, 27.71 mmol) in tetrahydrofuran (30.0 mL) were added sodium hydride (60% in mineral oil, 1.5 g, 38 mmol) and triisopropylsilyl chloride (8.0 mL, 38 mmol) under an atmosphere of nitrogen. The reaction was stirred for 2 hours at room temperature. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 10 % ethyl acetate in hexane to give compound (**47**, 3.0 g, 36%). MS(ESI)$[M+H^+]^+$ = 303.

[0111] 1-(tert-Butyl-dimethyl-silanyl)-3-iodo-1H-pyrrolo[2,3-b]pyridine **66**



was prepared following the protocol of Scheme 20 Step 2, substituting 1H-Pyrrolo[2,3-b]pyridine-3-carbaldehyde **46** with 3-iodo-1H-pyrrolo[2,3-b]pyridine and triisopropylsilyl chloride with tert-Butyl-dimethyl-silyl chloride.

[0112] 1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde **55**

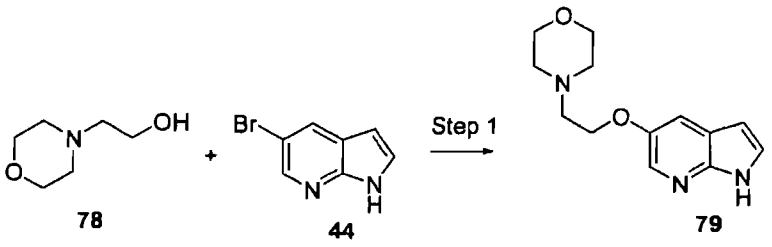


was prepared following the protocol of Scheme 20, substituting triisopropylsilyl chloride with benzenesulfonyl chloride in Step 2.

Example 3: Synthesis of 5 substituted 7-azaindole intermediates

[0113] 5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine **79** was synthesized in 1 Step from commercially available 5-bromo-azaindole as shown in Scheme 31.

Scheme 31



Step 1 – 5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine (**79**):

[0114] To 4-morpholineethanol (30 mL, 0.2 mol) in N, N-dimethylformamide (30 mL) was slowly added sodium hydride (7 g, 60% dispersion in mineral oil, 0.2 mol). After the solution turned clear, a solution of 5-bromo-7-azaindole (**44**, 1.0 g, 0.0051 mol) in N,N-dimethylformamide (5 mL) and copper(I) bromide (1.4 g, 0.0098 mol) were added. The reaction mixture was stirred at 120 °C under nitrogen for 2 hours. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate and water. The organic layer was collected, washed with a solution of ammonium chloride and ammonium hydroxide (4:1), brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as an off-white solid (**79**, 0.62 g, 50%). MS (ESI) $[M+H^+]^+ = 248.25$.

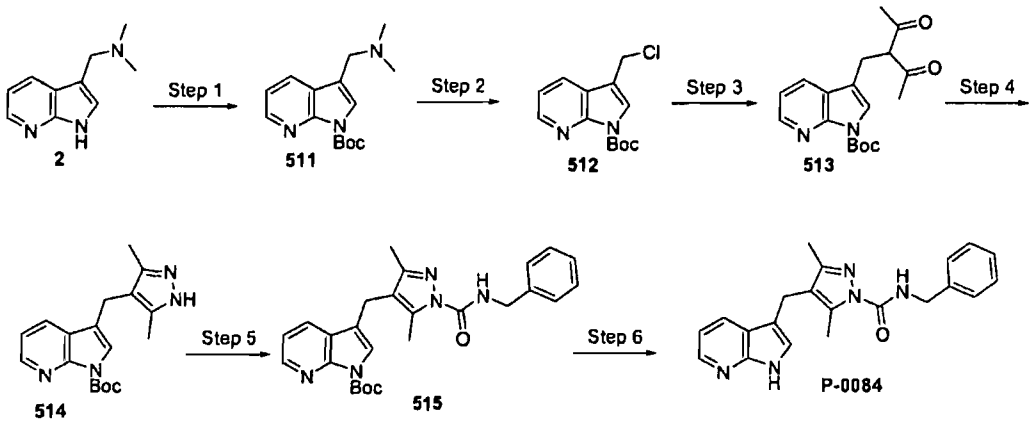
[0115] Additional 5-substituted 7-azaindoles were prepared following the protocol of Scheme 31, replacing 4-morpholineethanol with either 2-diethylamino-ethanol, 3-diethylamino-propan-1-ol, 2-piperidin-1-yl-ethanol, or 2-pyrrolidin-1-yl-ethanol to provide diethyl-[2-(1H-pyrrolo[2,3-

b]pyridin-5-yloxy)-ethyl]-amine, Diethyl-[3-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-propyl]-amine, 5-(2-piperidin-1-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine, and 5-(2-pyrrolidin-1-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine, respectively.

Example 4: Synthesis of 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid benzylamide P-0084

[0116] 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid benzylamide P-0084 was synthesized in 6 steps from dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine **2** as shown in Scheme 158.

Scheme – 158



Step 1: Preparation of 3-Dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (511)

[0117] To dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine (**2**, 2.50 g, 14.3 mmol,) in tetrahydrofuran (200.0 mL) was added sodium hydride (0.685 g, 60% in mineral oil, 17.1 mmol). After 10 minutes, di-*tert*-butyldicarbonate (3.74 g, 17.1 mmol) was added to the reaction. The reaction was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give as a white solid (**511**, 3.80 g, 96.7%).

Step 2: Preparation of 3-Chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (512)

[0118] To 3-dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**511**, 2.60 g, 9.44 mmol) in toluene (50.00 mL) was added isopropyl chloroformate (11.3 mL, 1.0 M in toluene) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 3

hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a white solid (**512**, 2.0 g, 79.4%).

Step 3 – Preparation of 3-(2-Acetyl-3-oxo-butyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (513):

[0119] To acetylacetone (0.563 g, 5.62 mmol) in dimethyl sulfoxide (29.0 mL) was added sodium hydride (0.225 g, 60% in mineral oil, 5.62 mmol). After 20 minutes, 3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**512**, 1.00 g, 3.75 mmol) was added to the reaction. The reaction was stirred at room temperature for 2 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 40% ethyl acetate in hexane to give a colorless oil (**513**, 0.59 g, 48.0%). MS (ESI) $[M+H^+]^+ = 331.4$.

Step 4 – Preparation of 3-(3,5-Dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (514)

[0120] To 3-(2-acetyl-3-oxo-butyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**513**, 1.20 g, 3.63 mmol) in methanol (15.0 mL), cooled to -20 °C under an atmosphere of nitrogen, was added hydrazine (0.128 g, 4.00 mmol) in dichloromethane (6.0 mL). The reaction was stirred for 2 hours. The reaction was concentrated to remove the solvents, and the residue was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 60% ethyl acetate in hexane to give a white solid (**514**, 1.0 g, 84.4%). MS (ESI) $[M+H^+]^+ = 327.4$.

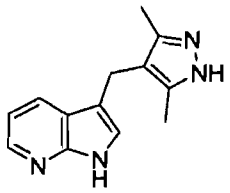
Step 5 – Preparation of 3-(1-Benzylcarbamoyl-3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (515)

[0121] To 3-(3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**514**, 60.0 mg, 0.18 mmol) in dichloromethane (6.0 mL) were added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.033 mL, 0.220 mmol) and benzyl isocyanate (29.4 mg, 0.220 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 2 hours. The reaction was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give crude compound (**515**, approx. 50 mg) that was used in the next step directly. MS (ESI) $[M+H^+]^+ = 460.5$.

Step 6 - 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid benzylamide (P-0084)

[0122] To 3-(1-benzylcarbamoyl-3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**515**, 50.0 mg, 0.11 mmol) in dichloromethane (6.0 mL) was added trifluoroacetic acid (0.20 mL, 2.6 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 20 minutes. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give a white solid (**P-0084**, 11.0 mg, 28.1%). MS (ESI) $[M+H^+]^+ = 360.5$.

[0123] 3-(3,5-Dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine **P-0124**



was prepared from 3-(3,5-Dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**514**, 15.0 mg, 0.046 mmol) by dissolving in dichloromethane (10.0 mL) to which trifluoroacetic acid (0.10 mL, 1.3 mmol) was added. The reaction was stirred at room temperature for 1 hour, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate in hexane to give an off-white solid (**P-0124**, 7.5 mg, 72.0%). MS (ESI) $[M+H^+]^+ = 227.3$.

[0124] Additional compounds were prepared following the protocol of Scheme 158, replacing dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine **2** with (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-dimethyl-amine (prepared as described in Example 10, Scheme 164, isolated after step 1) in Step 1 and replacing benzyl isocyanate with an appropriate electrophile in Step 5. The following compounds were made following this procedure:

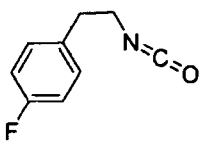
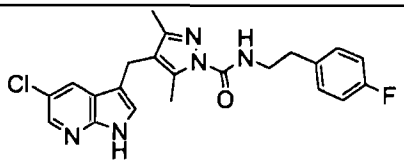
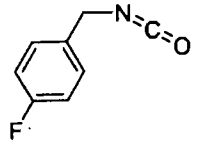
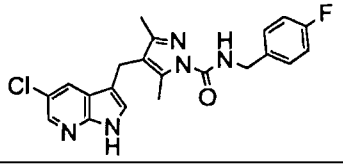
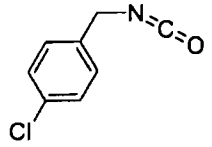
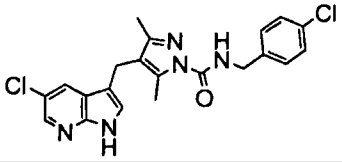
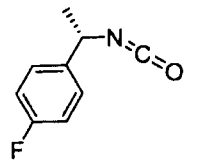
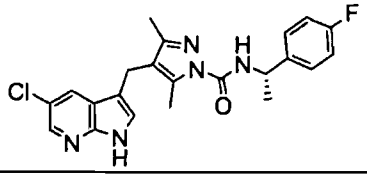
4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide (**P-0157**),

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid 4-fluoro-benzylamide (**P-0158**),

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid 4-chloro-benzylamide (**P-0159**), and

4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-3,5-dimethyl-pyrazole-1-carboxylic acid [(S)-1-(4-fluoro-phenyl)-ethyl]-amide (**P-0160**).

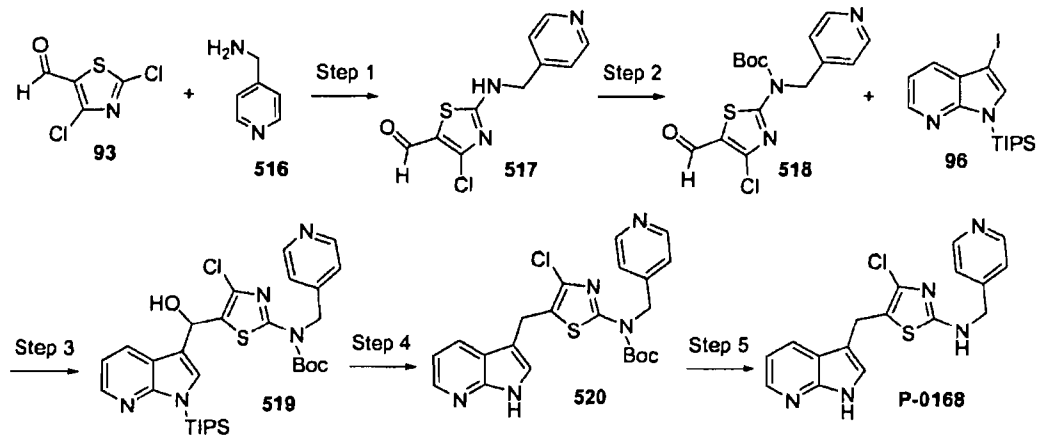
[0125] The electrophile used in place of benzyl isocyanate in Step 5 is indicated in Column 2 of the following table, with the compound structure given in Column 3. Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

	Electrophile	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0157			426.2
P-0158			412.2
P-0159			428.2
P-0160			426.2

Example 5: Synthesis of [4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine P-0168

[0126] [4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine **P-0168** was synthesized in 5 steps as shown in Scheme 159.

Scheme 159



Step 1 – Preparation of 4-chloro-2-[(pyridin-4-ylmethyl)-amino]-thiazole-5-carbaldehyde (517):

[0127] To a solution of 4-(aminomethyl)pyridine (**516**, 1.16 mL, 11.5 mmol) and N,N-diisopropylethylamine (3.8 mL, 22 mmol) in tetrahydrofuran (50 mL) was added 2,4-dichloro-thiazole-5-carbaldehyde (**93**, 2.0 g, 11.0 mmol) in tetrahydrofuran (5 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. The crude compound 4-chloro-2-[(pyridin-4-ylmethyl)-amino]-thiazole-5-carbaldehyde (**517**) was used for the next step without purification.

Step 2 – Preparation of (4-chloro-5-formyl-thiazol-2-yl)-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (518):

[0128] A mixture of 4-chloro-2-[(pyridin-4-ylmethyl)-amino]-thiazole-5-carbaldehyde (**517**, 3.28 g, 11.0 mmol), di-tert-butyldicarbonate (4.0 g, 18 mol) and triethylamine (10 mL, 74 mmol) in dichloromethane (120 mL) was stirred at room temperature for 6 hours. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexanes to provide the desired compound as a yellow solid (**518**, 564 mg, 15%). MS (ESI) $[M+H^+]^+ = 354.1$.

Step 3 – Preparation of {4-chloro-5-[hydroxy-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-thiazol-2-yl}-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (519):

[0129] To a solution of 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**96**, 0.44 g, 1.1 mmol) in tetrahydrofuran (20 mL) at -20 °C, isopropylmagnesium chloride (2 M in tetrahydrofuran, 0.6 mL, 1.2 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C in 10 minutes. The reaction mixture was then cooled to -40 °C. A solution of (4-

chloro-5-formyl-thiazol-2-yl)-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (**518**, 0.26 g, 0.73 mmol) in tetrahydrofuran (4 mL) was added to the reaction mixture. The reaction mixture was allowed to warm to -10 °C over 30 minutes. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexanes to provide the desired compound as a yellow solid (**519**, 397 mg, 86%). MS (ESI) $[M+H^+]^+ = 628.3$.

Step 4 – Preparation of [4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (520):

[0130] A mixture of {4-chloro-5-[hydroxy-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-thiazol-2-yl}-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (**519**, 0.397 g, 0.57 mmol), triethylsilane (1.0 mL, 6.3 mmol), and trifluoroacetic acid (0.5 mL, 6 mmol) in acetonitrile (10 mL) was stirred at 40 °C for 2 hours. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with sodium bicarbonate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide the desired compound as a yellow solid (**520**, 126 mg, 49%). MS (ESI) $[M+H^+]^+ = 456.2$.

Step 5 – Preparation of [4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine (P-0168):

[0131] To a solution of [4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (**520**, 126 mg, 0.000276 mol) in dichloromethane (2 mL) was added hydrogen chloride (4 M in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into cold sodium bicarbonate solution, extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. After removal of solvents, the residue was washed with ethyl acetate to provide the desired compound as a light yellow solid (**P-0168**, 68.4 mg, 70%). MS (ESI) $[M+H^+]^+ = 356.2$.

[0132] Additional compounds were prepared following the protocol of Scheme 159, replacing 4-(aminomethyl)pyridine **516** with an appropriate amine. The following compounds were made following this procedure:

[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine (**P-0164**),

[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-2-ylmethyl-amine (**P-0167**),

[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-amine (**P-0171**),

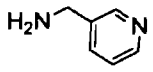
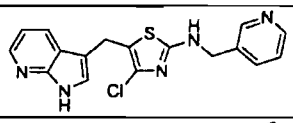
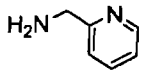
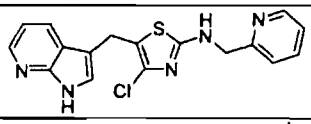
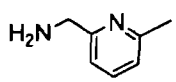
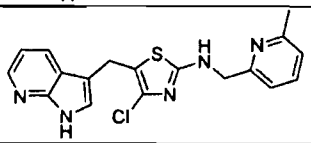
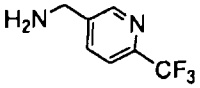
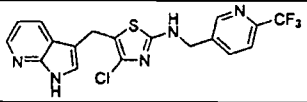
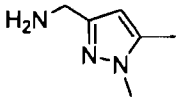
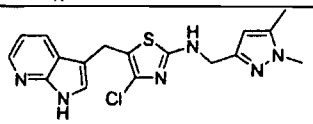
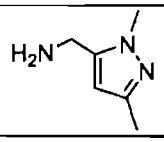
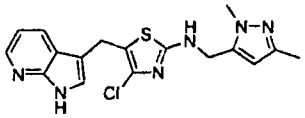
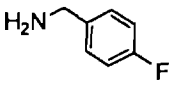
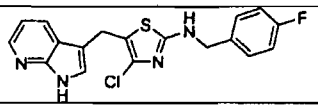
[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0173**),

[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-(1,5-dimethyl-1H-pyrazol-3-ylmethyl)-amine (**P-0172**),

[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-amine (**P-0175**), and

[4-Chloro-5-(1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine (**P-0156**).

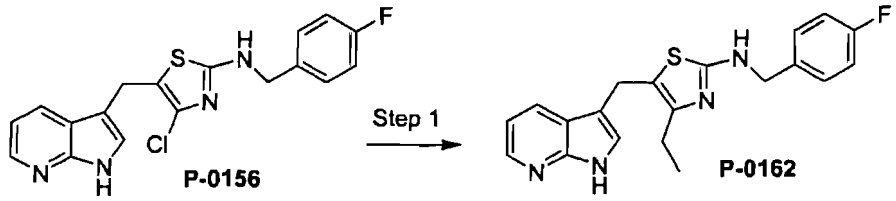
The following table indicates the amine (Column 2) used in Scheme 159 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the observed mass.

Compound number	Amine	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0164			356.1
P-0167			356.1
P-0171			370.2
P-0173			424.2
P-0172			373.2
P-0175			373.2
P-0156			373.1

Example 6: Synthesis of [4-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine P-0162 and (4-fluoro-benzyl)-[4-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine P-0162

[0133] [4-Ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **P-0162** was synthesized in 1 step from [4-chloro-5-(1H-pyrrolo[2, 3-b] pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **P-0156** as shown in Scheme 160.

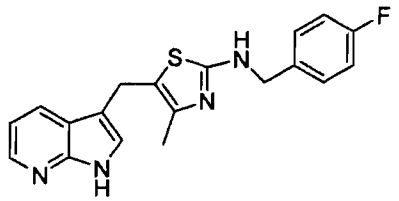
Scheme 160



*Step 1 – Preparation of [4-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine (**P-0162**):*

[0134] Into a round bottom flask, under an atmosphere of nitrogen, [1,1'-bis(diphenyl phosphino) ferrocene] dichloro palladium (II), complex with dichloromethane (1:1), was placed with toluene (15 mL, 140 mmol). [4-Chloro-5-(1H-pyrrolo[2,3-b] pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine (**P-0156**, 145 mg, 0.4 mmol) was added in 5 ml of toluene at room temperature. The mixture was stirred for 10 minutes. To the stirring reaction, a solution of 3.13 M ethyl magnesium bromide in ether (1.86 mL) was added dropwise at room temperature. The opaque solution was heated to 60 °C. Tetrahydrofuran (10 mL) was added to the warm solution. The mixture was heated to reflux for an additional two hours. After cooling to 0 °C, the reaction was quenched with a solution of citric acid at pH 4-5 in ice-water and stirred to room temperature. The mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Purification with flash chromatography, eluting with a gradient of ethyl acetate:hexanes (20:100), gave a yellow solid that was further washed with ethyl acetate to give **P-0162** (15 mg,10%) as an off-white solid. MS (ESI) $[M+H^+]^+ = 367.2$.

[0135] (4-Fluoro-benzyl)-[4-methyl-5-(1H-p yrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **P-0163**

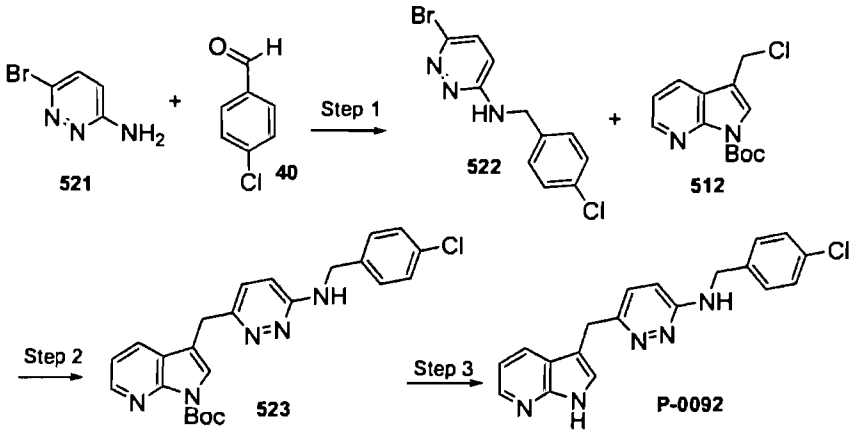


was prepared using the protocol of Scheme 160, substituting the 3.13 M ethyl magnesium bromide in ether solution with 1.4 M of methylmagnesium bromide in tetrahydrofuran. MS (ESI) $[M+H^+]^+$ = 353.2.

Example 7: Synthesis of (4-Chloro-benzyl)-[6-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridazin-3-yl]-amine P-0092

[0136] (4-Chloro-benzyl)-[6-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridazin-3-yl]-amine **P-0092** was synthesized in 3 steps as shown in Scheme 161.

Scheme 161



Step 1 – Synthesis of (6-bromo-pyridazin-3-yl)-(4-chloro-benzyl)-amine (522):

[0137] To 6-bromo-pyridazin-3-ylamine (**521**, 0.85 g, 0.0049 mol) in acetonitrile (30.0 mL) were added 4-chlorobenzaldehyde (**40**, 0.82 g, 0.0058 mol), triethylsilane (4.0 mL, 0.025 mol) and trifluoroacetic acid (2.0 mL, 0.026 mol). The reaction was heated to reflux for 4 hours, then poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and washed with ethyl acetate to give a white solid (**522**, 1.0 g). MS (ESI) $[M+H^+]^+$ = 298.3, 300.2.

Step 2 – Preparation of 3-[6-(4-chloro-benzylamino)-pyridazin-3-ylmethyl]-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (523):

[0138] To (6-bromo-pyridazin-3-yl)-(4-chloro-benzyl)-amine (**522**, 0.560 g, 1.88 mmol) in tetrahydrofuran (45.0 mL), under an atmosphere of nitrogen at -78 °C, was added n-butyllithium (2.50 M in hexane, 0.760 mL) slowly. After 10 minutes, 1,2-bis-(chloro-dimethyl-silanyl)-ethane (0.201 g, 0.94 mmol) in tetrahydrofuran (5.0 mL) was added to the reaction. The reaction mixture was allowed to stir at room temperature for 3 hours. The reaction was cooled to -78 °C, followed by addition of 1.70 M of tert-butyllithium in hexane (1.20 mL) slowly. The reaction was stirred for 20 minutes, followed by addition of a solution of CuCN.2LiCl (0.6 M in tetrahydrofuran, 3.00 mL) and 3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**512**, 0.47 g, 1.8 mol) in tetrahydrofuran (10.0 mL). After 30 minutes, the reaction was allowed to warm to room temperature for 10 minutes. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was treated with trifluoroacetic acid (1.0 mL) dissolved in dichloromethane (10.0 mL) for 10 minutes. The reaction was concentrated, poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified with silica gel column chromatography eluting with 60% ethyl acetate in hexane to give the desired compound (**523**, 0.10 g, 23.8%). MS (ESI) $[M+H^+]^+ = 450.1$.

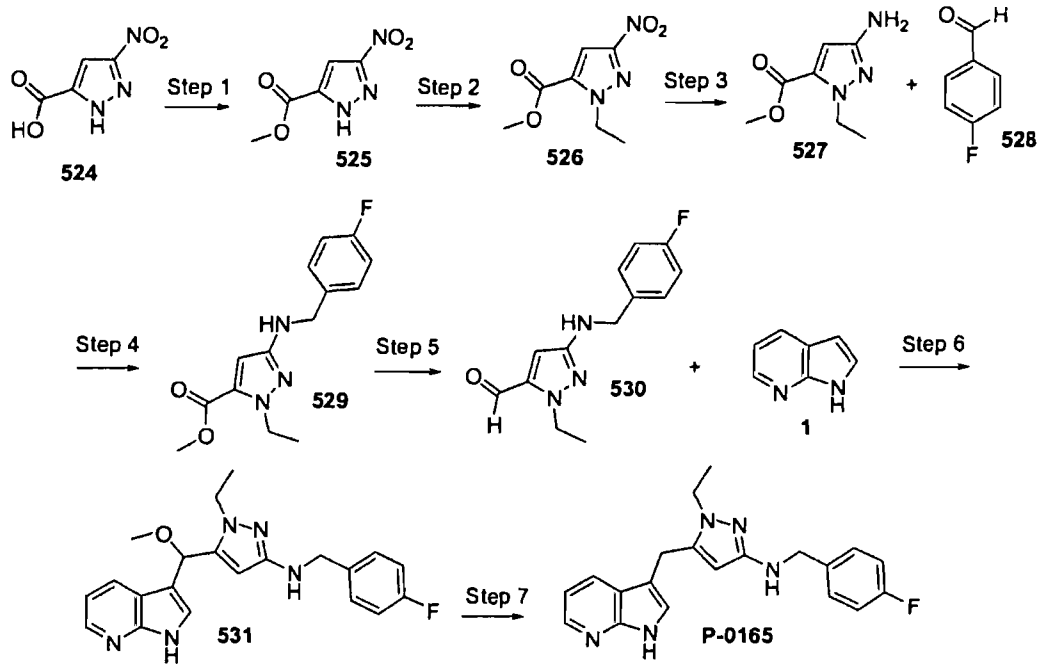
*Step 3 – Preparation of (4-chloro-benzyl)-[6-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridazin-3-yl]-amine (**P-0092**):*

[0139] To 3-[6-(4-chloro-benzylamino)-pyridazin-3-ylmethyl]-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**523**, 50.0 mg, 0.111 mmol) in dichloromethane (10.0 mL) was added trifluoroacetic acid (0.30 mL, 0.0039 mol). The reaction was stirred at room temperature overnight. The reaction was concentrated, poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate and hexane to give an off-white solid (**P-0092**, 7.3 mg, 19.0%). MS (ESI) $[M+H^+]^+ = 350.1$.

Example 8: Synthesis of [1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine P-0165

[0140] [1-Ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **P-0165** was synthesized in 7 steps as shown in Scheme 162.

Scheme 162



Step 1 – Preparation of 5-nitro-2H-pyrazole-3-carboxylic acid methyl ester (525):

[0141] To 5-nitro-2H-pyrazole-3-carboxylic acid (**524**, 10.0 g, 0.0637 mol) in methanol (100.0 mL) was added concentrated sulfuric acid (1.00 mL, 0.0180 mol). The reaction was stirred at room temperature overnight. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a white solid (**525**, 1.5 g, 13.8%).

Step 2 – Preparation of 2-ethyl-5-nitro-2H-pyrazole-3-carboxylic acid methyl ester (526):

[0142] To 5-nitro-2H-pyrazole-3-carboxylic acid methyl ester (**525**, 2.50 g, 0.0146 mol) in N,N-dimethylformamide (62.5 mL) were added iodoethane (1.2 mL, 0.016 mol) and potassium carbonate (4.17 g, 0.0301 mol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**526**, 1.3 g, 44.7%).

Step 3 – Preparation of 5-amino-2-ethyl-2H-pyrazole-3-carboxylic acid methyl ester (527):

[0143] To 2-ethyl-5-nitro-2H-pyrazole-3-carboxylic acid methyl ester (**526**, 1.30 g, 6.53 mmol) in methanol (60.0 mL) was added 20% $Pd(OH)_2/C$ (0.1 g). The reaction was stirred under an atmosphere of hydrogen overnight. The reaction was filtered and concentrated to give a light yellow solid (**527**, 1.0 g, 90.6%).

Step 4 – Preparation of 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carboxylic acid methyl ester (529):

[0144] To 5-amino-2-ethyl-2H-pyrazole-3-carboxylic acid methyl ester (**527**, 1.00 g, 5.91 mmol) in acetonitrile (27.5 mL) were added 4-fluorobenzaldehyde (**528**, 0.660 mL, 6.26 mmol), triethylsilane (4.77 mL, 0.0298 mol) and trifluoroacetic acid (2.38 mL, 0.0310 mol). The reaction was stirred at 80 °C for 4 hours, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**529**, 1.00 g, 61%).

Step 5 – Preparation of 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carbaldehyde (530):

[0145] To 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carboxylic acid methyl ester (**529**, 1.00 g, 3.61 mol) in tetrahydrofuran (70.0 mL) under an atmosphere of nitrogen at room temperature, lithium tetrahydroaluminate (1.00 M of in tetrahydrofuran, 10.00 mL) was slowly added. The reaction was stirred at room temperature overnight, followed by slowly adding sodium sulfate decahydrate (15.0 g). After 2 hours, the reaction was filtered, concentrated and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a yellow oil (**530**, 0.16 g, 18%). MS (ESI) $[M+H^+]^+ = 248.2$.

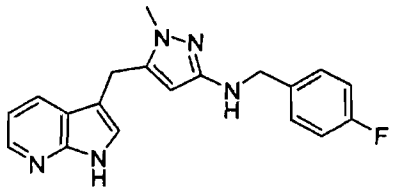
Step 6 – Preparation of 1-ethyl-5-[methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-1H-pyrazol-3-yl-(4-fluoro-benzyl)-amine (531):

[0146] To 1H-Pyrrolo[2,3-b]pyridine (**1**, 54.0 mg, 0.46 mmol) in methanol (15.0 mL) were added 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carbaldehyde (**530**, 110.0 mg, 0.44 mmol) and potassium hydroxide (0.60 g, 0.011 mol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 40% ethyl acetate in hexane to give a white solid (**531**, 0.12 g, 71.1%). MS (ESI) $[M-H^+]^- = 378.2$.

*Step 7 – Preparation of [1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine (**P-0165**):*

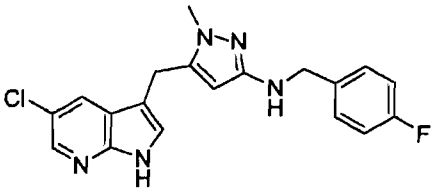
[0147] To 1-ethyl-5-[methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-1H-pyrazol-3-yl-(4-fluoro-benzyl)-amine (**531**, 0.12 g, 0.32 mmol) in acetonitrile (10.0 mL, 0.191 mol) were added trichylsilane (0.60 mL, 0.0038 mol) and trifluoroacetic acid (0.30 mL, 0.0039 mol). The reaction was stirred at 80 °C for 2 hours. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate and hexane to give crude compound. ^{1}H NMR indicated that the reaction was incomplete. The crude compound was dissolved in dichloromethane (15.0 mL), trifluoroacetic acid (0.30 mL) and triethylsilane (0.60 mL). The reaction was stirred at 43 °C for 72 hours. The reaction was concentrated, poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate and hexane to give an off-white solid (**P-0165**, 18.7 mg, 17%). MS (ESI) $[M+H^+]^+$ = 350.3.

[0148] (4-Fluoro-benzyl)-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-amine **P-0169**



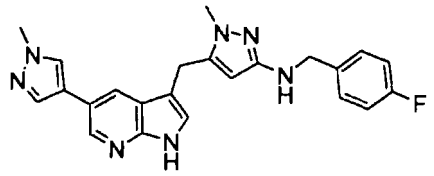
was prepared using the protocol of Scheme 162, substituting iodoethane with iodomethane in Step 2. MS (ESI) $[M+H^+]^+$ = 336.3.

[0149] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **P-0170**



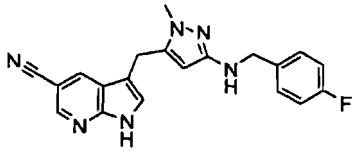
was prepared using the protocol of Scheme 162, substituting iodoethane with iodomethane in step 2 and 1H-pyrrolo[2,3-b]pyridine **1** with 5-chloro-1H-pyrrolo[2,3-b]pyridine in step 6. MS (ESI) $[M+H^+]^+$ = 370.3

[0150] (4-Fluoro-benzyl)-{1-methyl-5-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-1H-pyrazol-3-yl}-amine **P-0180**



was prepared using the protocol of Scheme 162, substituting iodoethane with iodomethane in step 2 and 1H-Pyrrolo[2,3-b]pyridine **1** with 5-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (prepared as described in Example 18, Scheme 172) in step 6. MS (ESI) $[M+H^+]^+ = 416.2$.

[0151] 3-[5-(4-Fluoro-benzylamino)-2-methyl-2H-pyrazol-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **P-0191**

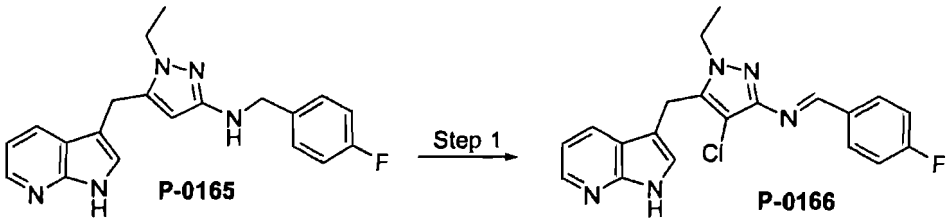


was prepared using the protocol of Scheme 162, substituting 1H-Pyrrolo[2,3-b]pyridine **1** with 1H-Pyrrolo[2,3-b]pyridine-5-carbonitrile in Step 6. MS (ESI) $[M+H^+]^+ = 361.5$.

Example 9: Synthesis of [4-chloro-1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-[1-(4-fluoro-phenyl)-meth-(E)-ylidene]-amine P-0166

[0152] [4-chloro-1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-[1-(4-fluoro-phenyl)-meth-(E)-ylidene]-amine **P-0166** was synthesized in 1 step as shown in Scheme 163.

Scheme 163



Step 1 – Preparation of [4-chloro-1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-[1-(4-fluoro-phenyl)-meth-(E)-ylidene]-amine (P-0166):

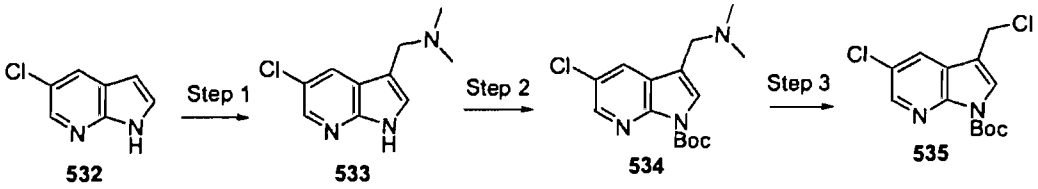
[0153] To [1-ethyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine (**P-0165**, 10.1 mg, 0.0289 mmol, prepared as described in Example 8, Scheme 162) in acetonitrile (8.0 mL) was added N-chloro-succinimide (4.18 mg, 0.0318 mmol). The reaction was stirred at room temperature for 2 hours. The reaction was concentrated and purified by silica gel

column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**P-0166**, 1.1 mg). MS (ESI) $[M+H^+]^+ = 382.1$.

Example 10: Synthesis of 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester

[0154] 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester was synthesized in 3 steps as shown in Scheme 164.

Scheme 164



Step 1 – Preparation of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-dimethyl-amine (533):

[0155] To 5-Chloro-1H-pyrrolo[2,3-b]pyridine (**532**, 8.00 g, 0.0524 mol) in isopropyl alcohol (250.0 mL) were added dimethylamine hydrochloride (4.79 g, 0.0587 mol) and formaldehyde (1.77 g, 0.0589 mol). The reaction was stirred at room temperature overnight, followed by refluxing for 4 hours. The reaction was concentrated, poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give crude compound (**533**, 10.0 g, 91%), that was used directly in the next step.

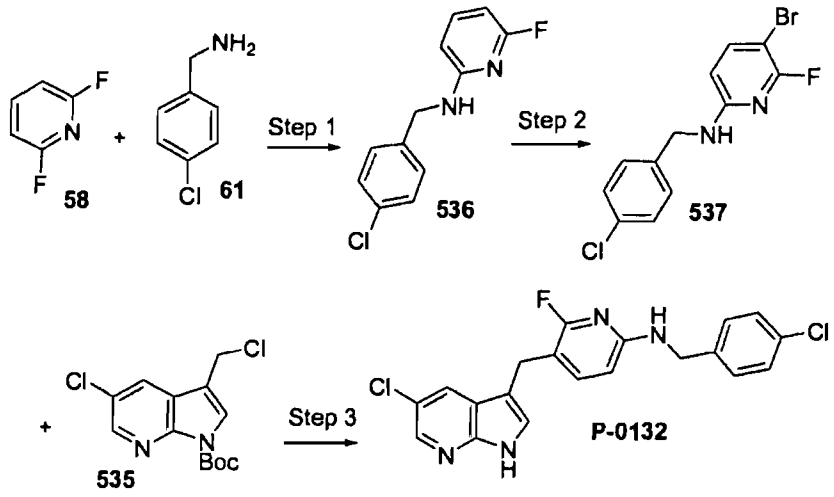
Step 2 and 3 – Preparation of 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (535):

[0156] 5-Chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester **535** was prepared following the protocol of Scheme 158 (Example 4) steps 1 and 2, substituting dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine **2** with (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-dimethyl-amine **533** in step 1.

Example 11: Synthesis of (4-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-amine P-0132

[0157] (4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-amine **P-0132** was synthesized in 3 steps as shown in Scheme 165.

Scheme 165



Step 1 – Preparation of (4-chloro-benzyl)-(6-fluoro-pyridin-2-yl)-amine (536):

[0158] To 2,6-difluoropyridine (**58**, 9.85 g, 0.0856 mol) in N-methylpyrrolidinone (50.0 mL) were added p-chlorobenzylamine (**61**, 10.5 mL, 8.63 mmol) and N,N-diisopropylethylamine (30.0 mL, 0.172 mol). The reaction was stirred at 90 °C overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 25% ethyl acetate in hexane, then washed with ethyl acetate/hexane to give a white solid (**536**, 10 g, 50%).

Step 2 – Preparation of (5-bromo-6-fluoro-pyridin-2-yl)-(4-chloro-benzyl)-amine (537):

[0159] To (4-chloro-benzyl)-(6-fluoro-pyridin-2-yl)-amine (**536**, 1.03 g, 4.35 mmol) in acetonitrile (30.0 mL), under an atmosphere of nitrogen, N-bromosuccinimide (0.820 g, 4.61 mol) was added slowly. After 2 hours, the reaction was poured into a solution of sodium thiosulfate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and crytstallized with ethyl acetate and hexane to give a white solid (**537**, 1.10 g, 80.1%).

*Step 3 – Preparation of (4-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-amine (**P-0132**):*

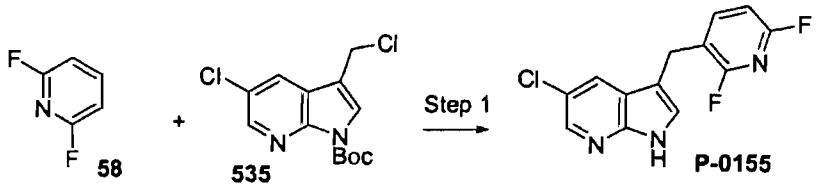
[0160] To (5-bromo-6-fluoro-pyridin-2-yl)-(4-chloro-benzyl)-amine (**537**, 2.76 g, 8.75 mol) in tetrahydrofuran (90.0 mL), under an atmosphere of nitrogen at -78 °C, n-butyllithium (2.50 M in hexane, 3.64 mL) was added slowly. After 60 minutes, 1,2-bis-(chloro-dimethyl-silanyl)-ethane (0.942 g, 4.38 mol) in tetrahydrofuran (8.0 mL) was added to the reaction. The reaction mixture was allowed to stir at room temperature for 2 hours. The reaction was cooled to -78 °C, followed by addition of tert-butyllithium (1.70 M in hexane, 10.50 mL). The reaction was stirred for 30

minutes, followed by addition of 0.65 M of CuCN.2LiCl in tetrahydrofuran (14.0 mL). The reaction was stirred at -35 °C for 10 minutes, followed by addition of 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**535**, 1.70 g, 5.64 mol, prepared as described in Example 10, Scheme 164) in tetrahydrofuran (10.0 mL). The reaction was allowed to warm to room temperature for 1 hour and 2 N HCl (30 mL) was added to the reaction mixture, then stirred for 30 minutes. The reaction was poured into aqueous ammonia and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified with silica gel column chromatography eluting with 30% ethyl acetate in hexane to give the desired compound (**P-0132**, 0.75 g, 33.1%). MS (ESI) $[M+H^+]^+$ = 401.1.

Example 12: Synthesis of 5-chloro-3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine P-0155

[0161] 5-Chloro-3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **P-0155** was synthesized in 1 step as shown in Scheme 166.

Scheme 166



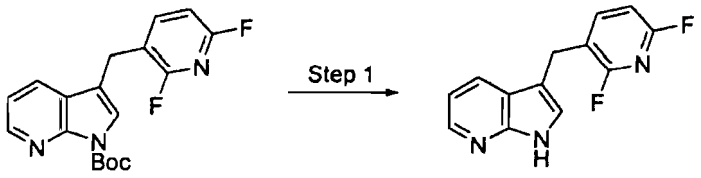
Step 1 – Preparation of 5-chloro-3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (P-0155):

[0162] To 2,6-Difluoropyridine (**58**, 3.40 g, 0.0295 mol) in tetrahydrofuran (200.0 mL), under an atmosphere of nitrogen at -78 °C, 2.50 M of n-butyllithium in hexane (12.0 mL) was added slowly. After 60 minutes, CuCN.2LiCl (0.75 M in tetrahydrofuran, 40.0 mL) was added to the reaction mixture. After 5 minutes, 5-chloro-3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**535**, 4.20 g, 0.0139 mol, prepared as described in Example 10, Scheme 164) in tetrahydrofuran (20 mL) was added to the reaction. The reaction was stirred at -78 °C overnight, then poured into water and ammonia (10 mL), and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 15% ethyl acetate in hexane to give a white solid (**P-0155**, 300 mg, 7.7%). MS (ESI) $[M-H^+]^-$ = 278.1.

Example 13: Synthesis of 3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine P-0154

[0163] 3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **P-0154** was synthesized in 1 step as shown in Scheme 167.

Scheme 167



536 **P-0154**

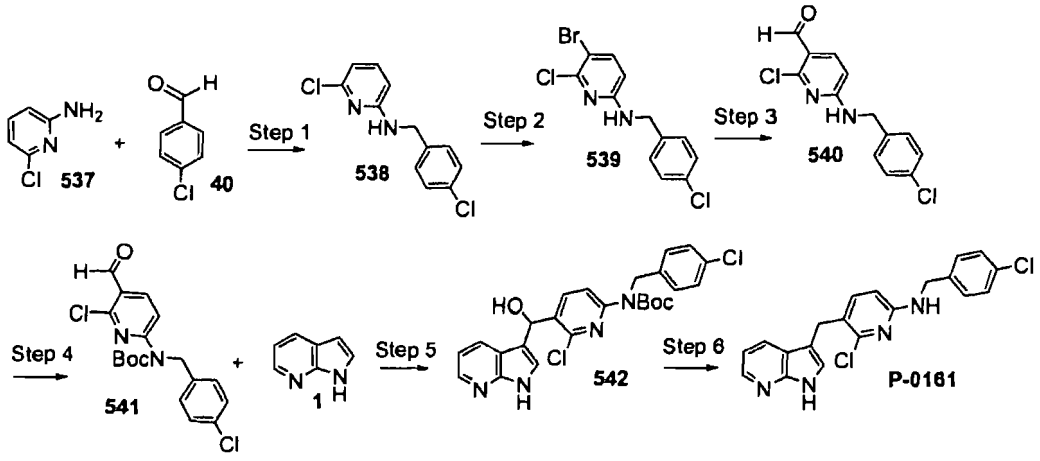
Step 1 – Preparation of 3-(2,6-difluoro-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (P-0154):

[0164] To 3-(2,6-difluoro-pyridin-3-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**536**, 0.35 g, 1.0 mmol, prepared as described in Example 10, Scheme 164, replacing 5-chloro-1H-pyrrolo[2,3-b]pyridine **532** with 1H-pyrrolo[2,3-b]pyridine in step 1) in N-methylpyrrolidinone (3.00 mL) were added p-chlorobenzylamine (0.20 mL, 1.6 mmol) and N,N-diisopropylethylamine (0.30 mL, 0.0017 mol). The reaction was stirred at 50 °C for 72 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and the crude intermediate was dissolve in dichloromethane (15.0 mL) and trifluoroacetic acid (0.5 mL). The reaction was stirred at room temperature for 2 hours, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 35% ethyl acetate in hexane to give a white solid (**P-0154**, 0.18 g, 72%). MS (ESI) $[M+H^+]^+ = 246.2$.

Example 14: Synthesis of 5-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-N-(4-chlorobenzyl)-6-chloropyridin-2-amine P-0161

[0165] 5-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-N-(4-chlorobenzyl)-6-chloropyridin-2-amine **P-0161** was synthesized in 6 steps as shown in Scheme 168.

Scheme 168



Step 1 - Preparation of (4-chloro-benzyl)-(6-chloro-pyridin-2-yl)-amine (538):

[0166] To 6-chloro-pyridin-2-ylamine (**537**, 5.60 g, 0.0436 mol) in acetonitrile (300 mL) were added 4-chlorobenzaldehyde (**40**, 6.7 g, 0.048 mol), trifluoroacetic acid (13 mL, 0.17 mol) and triethylsilane (21 mL, 0.13 mol). The reaction was heated to reflux for 4 hours, then concentrated, poured into water, extracted with ethyl acetate, and washed with sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The filtrate was purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**538**, 6.5 g, 59%). MS (ESI) $[M+H^+]^+ = 255.1$.

Step 2 – Preparation of (5-bromo-6-chloro-pyridin-2-yl)-(4-chloro-benzyl)-amine (539):

[0167] To (4-chloro-benzyl)-(6-chloro-pyridin-2-yl)-amine (**538**, 4.00 g, 0.0158 mol) in acetonitrile (66.7 mL, 1.28 mol) under an atmosphere of nitrogen, N-bromosuccinimide (2.81 g, 0.0158 mol) in acetonitrile (20 mL) was added slowly. The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and crystallized with ethyl acetate in hexane to give a white solid (**539**, 2.60 g, 95.3%).

Step 3 – Preparation of 2-chloro-6-(4-chloro-benzylamino)-pyridine-3-carbaldehyde (540):

[0168] To (5-bromo-6-chloro-pyridin-2-yl)-(4-chloro-benzyl)-amine (**539**, 2.60 g, 7.83 mmol) in tetrahydrofuran (60.0 mL) under an atmosphere of nitrogen at -78 °C, isopropylmagnesium chloride (2.00 M in tetrahydrofuran, 4.20 mL) was added over 10 minutes. The reaction was stirred at -78 °C for 20 minutes, then allowed to warm to room temperature for 10 minutes. The reaction was cooled to -78 °C. tert-Butyllithium (1.70 M in hexane, 10.2 mL) was added to the reaction over 10 minutes. After 40 minutes, N,N-dimethylformamide (1.80 mL, 0.0232 mol) was added to the reaction. The reaction was stirred at -78 °C for 40 minutes, then allowed to warm to

room temperature for another 30 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 35% to 100% ethyl acetate in hexane to give a light yellow solid (**540**, 1.0 g, 45.4%). MS (ESI) $[M-H^+]^-$ = 279.0.

Step 4 – Preparation of (4-chloro-benzyl)-(6-chloro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (541):

[0169] To 2-chloro-6-(4-chloro-benzylamino)-pyridine-3-carbaldehyde (**540**, 0.40 g, 1.42 mmol) in dichloromethane (10.0 mL) were added 4-dimethylaminopyridine (10.0 mg, 0.082 mmol), di-tert-butyldicarbonate (0.693 g, 3.17 mmol) and triethylamine (0.50 mL, 0.0036 mol). The reaction was stirred at room temperature overnight, then concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**541**, 0.45 g, 83.0%).

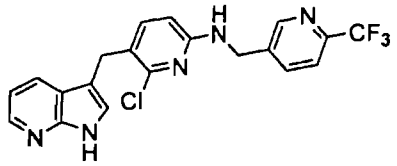
Step 5 – Preparation of (4-chloro-benzyl)-6-chloro-5-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl-carbamic acid tert-butyl ester (542):

[0170] To 1H-Pyrrolo[2,3-b]pyridine (**1**, 465 mg, 3.93 mmol) in methanol (50 mL) were added sodium hydroxide (0.630 g, 0.0157 mol) and (4-chloro-benzyl)-(6-chloro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**541**, 1.5 g, 0.0039 mol). The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**542**, 1.0g, 51%). MS (ESI) $[M+H^+]^+$ = 499.1.

Step 6 – Preparation of 5-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-N-(4-chlorobenzyl)-6-chloropyridin-2-amine (P-0161):

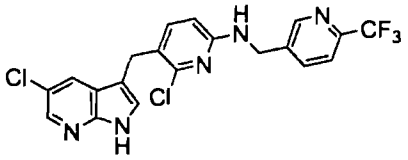
[0171] To (4-chloro-benzyl)-6-chloro-5-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl-carbamic acid tert-butyl ester (**542**, 1.00 g, 2.00 mmol) in acetonitrile (130.0 mL) were added triethylsilane (11.5 mL, 0.0720 mol) and trifluoroacetic acid (5.5 mL, 0.071 mol). The reaction was heated to reflux for 2 hours, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate and hexane to give a light yellow solid (**P-0161**, 480 mg, 62%). MS (ESI) $[M+H^+]^+$ = 383.1, 385.1.

[0172] [6-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0174**



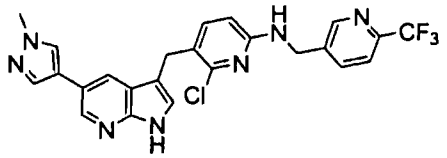
was prepared following the protocol of Scheme 168, substituting 4-chloro-benzaldehyde **40** with 6-trifluoromethyl-pyridine-3-carbaldehyde in step 1. MS (ESI) $[M+H^+]^+ = 418.2$.

[0173] [6-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0176**



was prepared following the protocol of Scheme 168, substituting 4-chloro-benzaldehyde **40** with 6-trifluoromethyl-pyridine-3-carbaldehyde in step 1 and 1H-Pyrrolo[2,3-b]pyridine **1** with 5-chloro-1H-pyrrolo[2,3-b]pyridine in step 5. MS (ESI) $[M+H^+]^+ = 452.0$.

[0174] {6-Chloro-5-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0179**

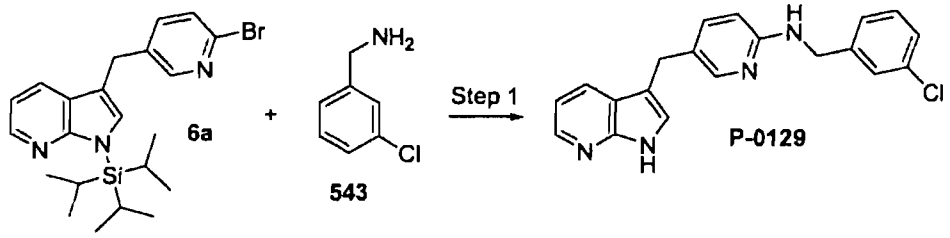


was prepared following the protocol of Scheme 168, substituting 4-chloro-benzaldehyde **40** with 6-trifluoromethyl-pyridine-3-carbaldehyde in step 1 and 1H-Pyrrolo[2,3-b]pyridine **1** with 5-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (prepared as described in Example 18, Scheme 172) in step 5. MS (ESI) $[M+H^+]^+ = 498.0$.

Example 15: Synthesis of (3-chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0129

[0175] (3-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0129** was synthesized in 1 step as shown in Scheme 169.

Scheme 169



Step 1 – Preparation of (3-chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0129):

[0176] 3-(6-bromo-pyridin-3-ylmethyl)-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**6a**, 10 mg, 0.023 mmol) was combined with 3-chlorobenzyl amine (**543**, 13 mg, 0.093 mmol) in dioxane (0.3 mL). Tris(dibenzylideneacetone)-dipalladium(0) (3 mg), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 3 mg) and sodium *tert*-butoxide (15 mg) were added. The mixture was heated at 100 °C overnight. Acetic acid (0.1 mL) was added and the solvents removed under reduced pressure. The remaining residue was dissolved in DMSO and purified by reverse phase HPLC on a YMC-Pack ODS-A C-18 column (50mm x 10mm ID), eluting with water with 0.1 % trifluoroacetic acid and 5-40% acetonitrile with 0.1% trifluoroacetic acid over 13 minutes at a flow rate of 6 mL/minute to provide the desired compound **P-0129**. MS (ESI) $[M+H^+]^+ = 349.1$.

[0177] Additional compounds were prepared following the protocol of Scheme 169, replacing 3-chlorobenzyl amine **543** with an appropriate amine. The following compounds were made following this procedure:

(4-Morpholin-4-ylmethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0093**),

Pyridin-3-ylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0094**),

(5-Methyl-isoxazol-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0095**),

(2-Pyrrolidin-1-yl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0096**),

[1-(4-Methanesulfonyl-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0097**),

(2-Methoxy-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0098**),

(2-Morpholin-4-yl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0099**),

((R)-1-Phenyl-ethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0125**),

(3-Morpholin-4-yl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0126**),

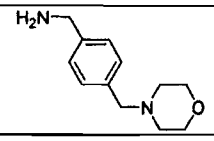
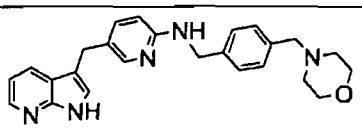
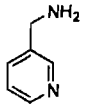
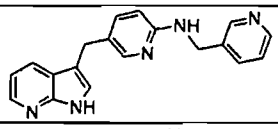
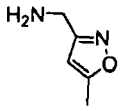
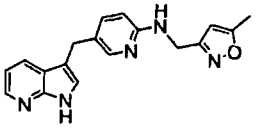
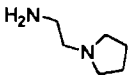
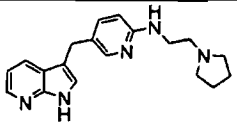
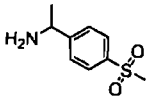
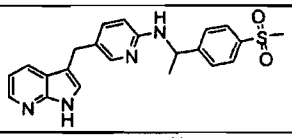
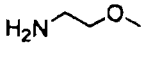
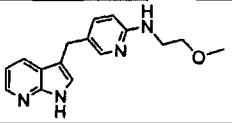
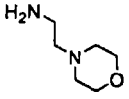
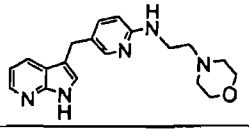
[1-(2-Fluoro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0127**),

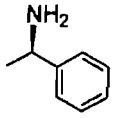
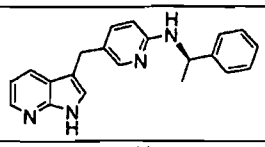
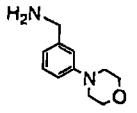
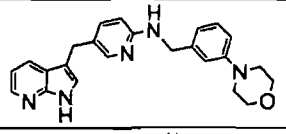
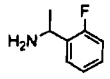
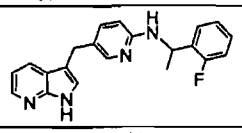
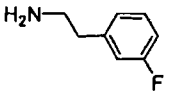
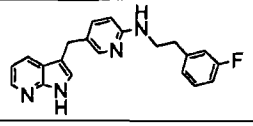
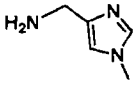
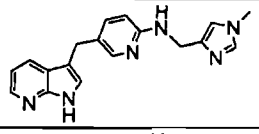
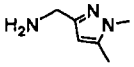
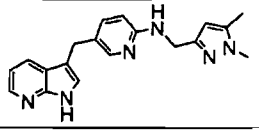
[2-(3-Fluoro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0128**),

(1-Methyl-1H-imidazol-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0130**), and

(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0131**).

[0178] The following table indicates the amine (Column 2) used in Scheme 169 to provide the compounds (Column 3). Column 1 provides the compound number and column 4 the observed mass.

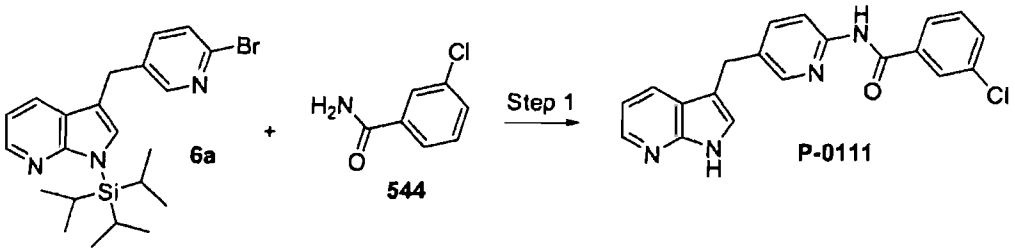
Compound number	Amine	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0093			414.3
P-0094			316.3
P-0095			319.9
P-0096			322.3
P-0097			407.1
P-0098			283.5
P-0099			338.3

Compound number	Amine	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0125			329.1
P-0126			400.3
P-0127			347.1
P-0128			347.1
P-0130			319.1
P-0131			333.1

Example 16: Synthesis of 3-chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide P-0111

[0179] 3-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide **P-0111** was synthesized in 1 step as shown in Scheme 170.

Scheme 170



*Step 1 – Preparation of 3-chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0111**):*

[0180] 3-(6-Bromo-pyridin-3-ylmethyl)-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**6a**, 10 mg, 0.023 mmol) was combined with 3-chloro-benzamide (**544**, 15 mg, 0.096 mmol) in dioxane (0.4 mL). Tris(dibenzylideneacetone)-dipalladium(0) (3 mg), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 3 mg), and sodium *tert*-butoxide (15 mg) were added. Cesium carbonate (20 mg) was added and the mixture was heated at 100 °C overnight. Acetic acid (0.1 mL) was added and the solvents removed under reduced pressure. The remaining residue was dissolved in DMSO (0.2 mL) and purified by reverse phase HPLC on a YMC-Pack ODS-A C-18 column (50mm x 10mm ID), eluting with water with 0.1 % trifluoroacetic acid and 5-40% acetonitrile with 0.1% trifluoroacetic acid over 13 minutes at a flow rate of 6 mL/minute to provide the desired compound **P-0111**. MS (ESI) $[M+H^+]^+ = 363.1$.

[0181] Additional compounds were prepared following the protocol of Scheme 170, replacing 3-chloro-benzamide **544** with an appropriate amide. The following compounds were made following this procedure:

3,4-Dichloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0100**),

2-Chloro-4-fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0101**),

2,5-Dimethyl-2H-pyrazole-3-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0102**),

Thiophene-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0103**),

2-Methoxy-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0104**),

N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0105**),

Pyrazine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0106**),

Pyridine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0107**),

6-Methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-nicotinamide (**P-0108**),

4-Fluoro-3-methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0109**),

5-Methyl-pyrazine-2-carboxylic acid [5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amide (**P-0110**),

4-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethyl-benzamide (**P-0112**),

N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethoxy-benzamide (**P-0113**),

N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-trifluoromethyl-benzamide (**P-0114**),

3-Chloro-4-fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0115**),

3,4-Difluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0116**),

2-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0117**),

5-Fluoro-2-methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0118**),

2-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0119**),

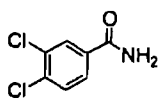
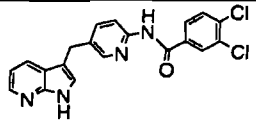
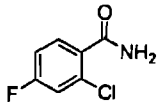
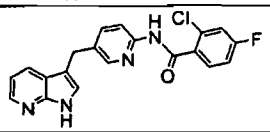
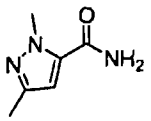
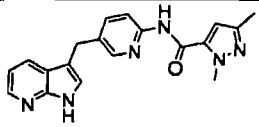
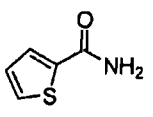
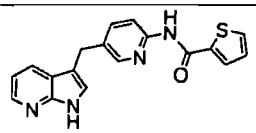
3-Methoxy-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0120**),

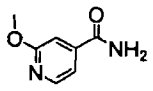
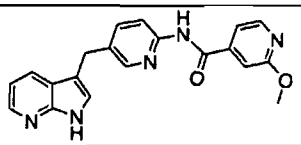
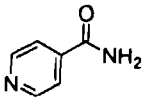
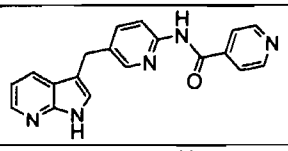
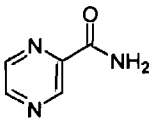
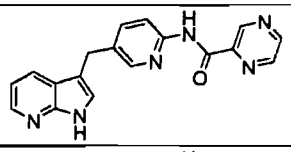
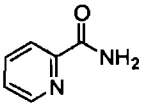
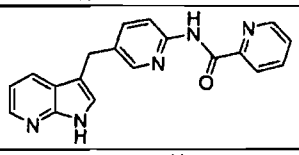
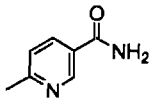
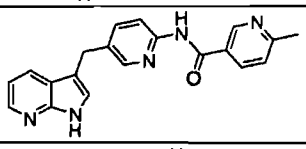
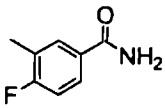
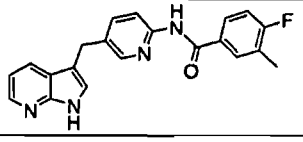
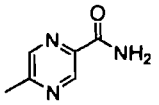
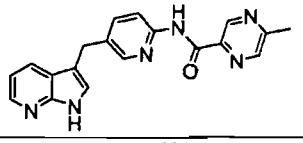
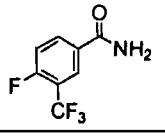
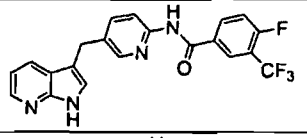
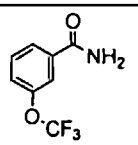
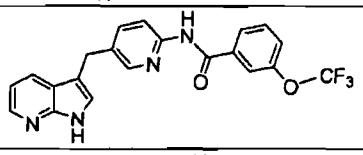
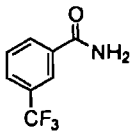
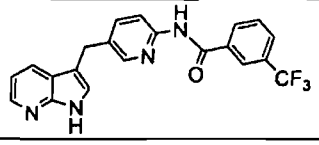
3-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0121**),

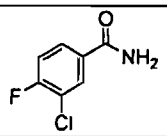
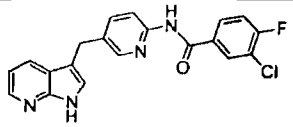
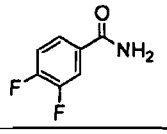
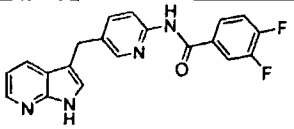
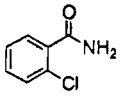
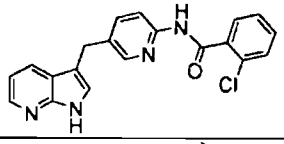
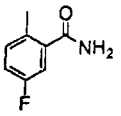
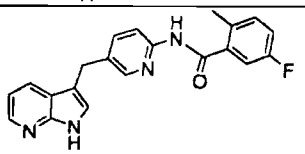
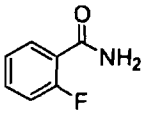
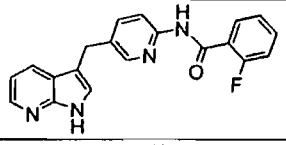
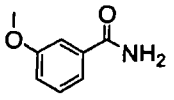
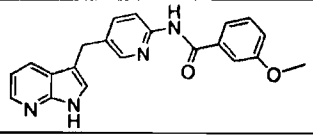
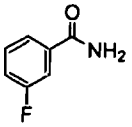
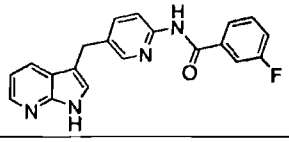
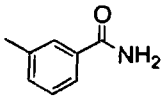
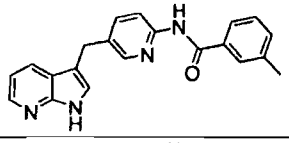
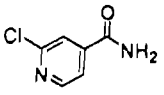
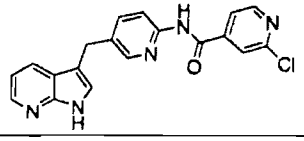
3-Methyl-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (**P-0122**), and

2-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-isonicotinamide (**P-0123**).

[0182] The following table indicates the amide (Column 2) used in Scheme 170 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the observed mass.

Compound number	Amide	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0100			397.1
P-0101			381.1
P-0102			347.1
P-0103			335.1

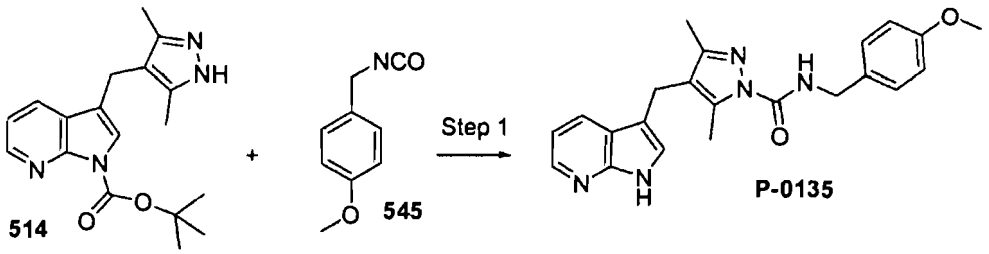
Compound number	Amide	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0104			360.3
P-0105			329.9
P-0106			331.1
P-0107			329.9
P-0108			344.3
P-0109			361.1
P-0110			345.1
P-0112			415.1
P-0113			413.1
P-0114			397.1

Compound number	Amide	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0115			381.1
P-0116			365.1
P-0117			363.1
P-0118			361.1
P-0119			347.1
P-0120			359.1
P-0121			347.1
P-0122			343.1
P-0123			364.3

Example 17: Synthesis of 3,5-dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methoxy-benzylamide P-0135

[0183] 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methoxy-benzylamide **P-0135** was synthesized in 1 step as shown in Scheme 171.

Scheme 171



Step 1 – Preparation of 3,5-dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methoxy-benzylamide (P-0135):

[0184] 3-(3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**514**, 10 mg, 0.03 mmol) was dissolved in dichloromethane (0.5 mL). 1,8-Diazabicylo[5.4.0]unde-7-ene (6 mg, 0.04 mmol) was added. 1-Isocyanatomethyl-4-methoxy-benzene (**545**, 6.5 mg, 0.04 mmol) was added. The reaction was allowed to proceed at room temperature for 30 minutes. Acetic acid (0.2 mL) was added to the reaciton. The solvents were removed under reduced pressure. The residue was dissolved in dimethyl sulfoxide (0.2 mL) and purified by reverse phase HPLC on a Phenomenex column (50mm x 10mm ID), eluting with water with 0.1 % trifluoroacetic acid and 20-100% acetonitrile with 0.1% trifluoroacetic acid over 16 minutes at a flow rate of 6 mL/minute to provide the desired compound **P-0135**. MS (ESI) $[M+H^+]^+ = 390.3$.

[0185] Additional compounds were prepared following the protocol of Scheme 171, replacing 1-isocyanatomethyl-4-methoxy-benzene **545** with an appropriate isocyanate or bromide. The following compounds were made following this procedure:

3-(1-Benzyl-3,5-dimethyl-1H-pyrazol-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**P-0133**),

2-[3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazol-1-yl]-1-phenyl-ethanone (**P-0134**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-chloro-benzylamide (**P-0136**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-fluoro-benzylamide (**P-0137**),

3-[3,5-Dimethyl-1-(5-trifluoromethyl-furan-2-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (**P-0138**),

3-[3,5-Dimethyl-1-(5-methyl-isoxazol-3-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (**P-0139**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-chloro-benzylamide (**P-0140**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(4-ethoxy-phenyl)-ethyl]-amide (**P-0141**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 3-methoxy-benzylamide (**P-0142**),

3-{3,5-Dimethyl-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyl]-1H-pyrazol-4-ylmethyl}-1H-pyrrolo[2,3-b]pyridine (**P-0143**),

3-[3,5-Dimethyl-1-(4-methyl-2-phenyl-thiazol-5-ylmethyl)-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (**P-0144**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-methoxy-benzylamide (**P-0145**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide (**P-0146**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide (**P-0147**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid [2-(2-fluoro-phenyl)-ethyl]-amide (**P-0148**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid ((S)-1-phenyl-ethyl)-amide (**P-0149**),

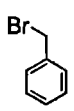
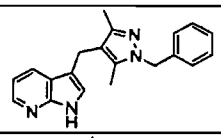
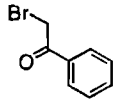
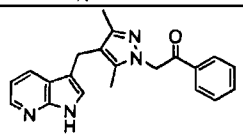
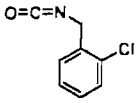
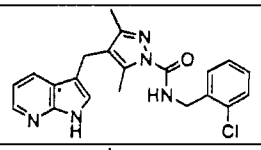
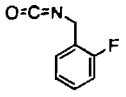
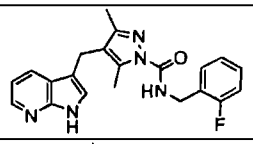
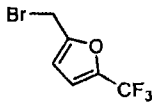
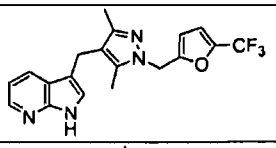
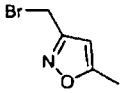
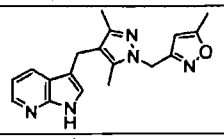
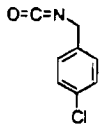
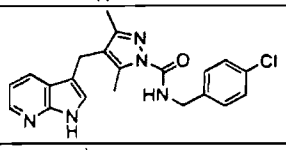
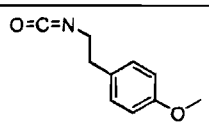
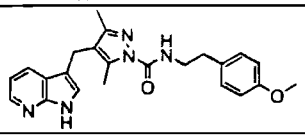
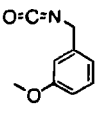
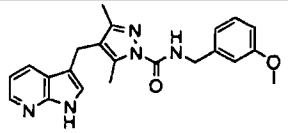
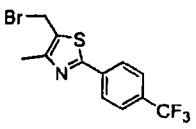
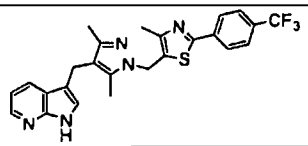
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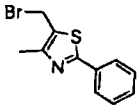
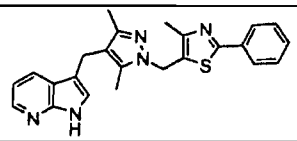
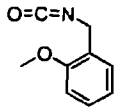
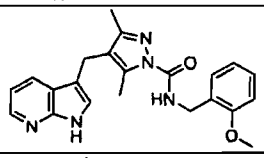
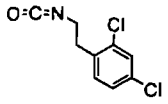
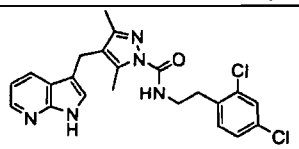
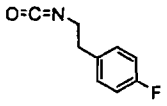
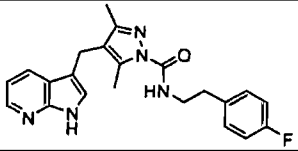
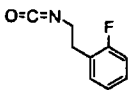
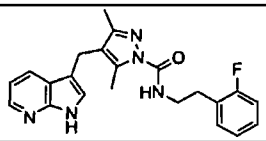
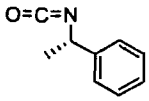
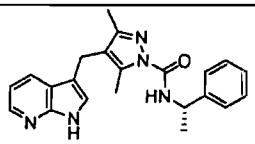
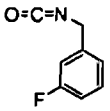
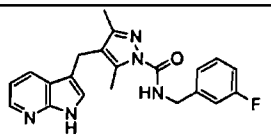
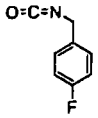
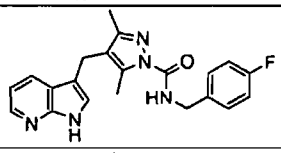
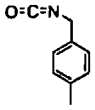
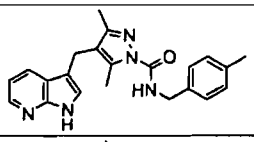
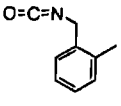
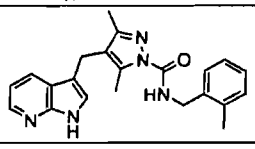
3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-fluoro-benzylamide (**P-0151**),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 4-methyl-benzylamide (**P-0152**), and

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid 2-methyl-benzylamide (**P-0153**).

[0186] The following table indicates the isocyanate or bromide (Column 2) used in Scheme 171 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the observed mass.

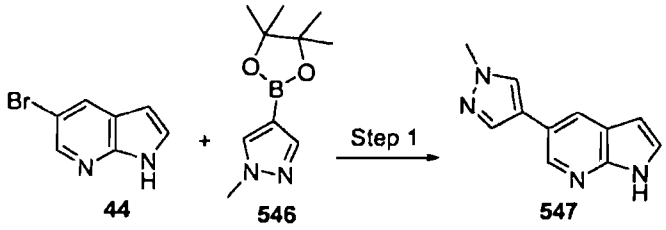
Compound number	Isocyanate or bromide	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0133			317.1
P-0134			345.1
P-0136			394.3
P-0137			378.3
P-0138			375.1
P-0139			322.3
P-0140			393.9
P-0141			404.3
P-0142			390.3
P-0143			482.3

Compound number	Isocyanate or bromide	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0144			414.3
P-0145			390.3
P-0146			442.3
P-0147			392.3
P-0148			392.3
P-0149			374.3
P-0150			378.3
P-0151			378.3
P-0152			374.3
P-0153			374.3

Example 18: Synthesis of 5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine 547.

[0187] 5-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **547** was synthesized in 1 step from 5-bromo-1H-pyrrolo[2,3-b]pyridine **44** as shown in Scheme 172.

Scheme 172



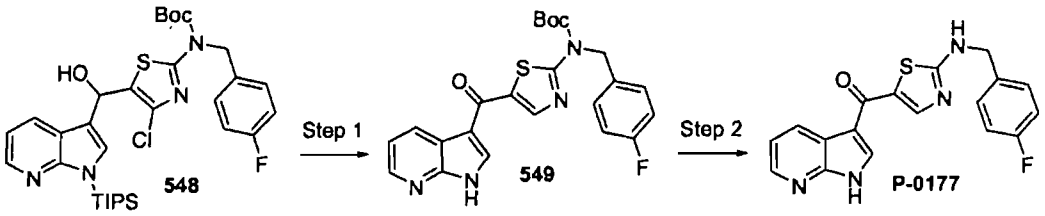
Step 1 – Preparation of 5-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**547**):

[0188] To 5-bromo-7-azaindole (**44**, 1.04 g, 5.28 mmol) in 1.00 M potassium carbonate in water (15.8 mL) and tetrahydrofuran (50.0 mL) were added 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (**546**, 1.65 g, 7.92 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.305 mg, 0.26 mmol) and tetra-n-butylammonium iodide (0.20 g, 0.53 mmol). The reaction mixture was stirred at 70 °C overnight. The reaction mixture was poured into water and the organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified with silica gel column chromatography eluting with 25% ethyl acetate in hexane to provide a light yellow solid (**547**, 670 mg, 64.0%). MS(ESI)$[M+H^+]^+$ = 199.4.

Example 19: Synthesis of [2-(4-fluoro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-0177.

[0189] [2-(4-Fluoro-benzylamino)-thiazol-5 -yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0177** was synthesized in 2 steps as shown in Scheme 173.

Scheme 173



Step 1 – Preparation of(4-fluoro-benzyl)-[5-(1H-pyrrolo[2, 3-b]pyridine-3-carbonyl)-thiazol-2-yl]-carbamic acid tert-butyl ester (549):

[0190] A mixture of {4-chloro-5-[hydroxy-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-thiazol-2-yl}-pyridin-4-ylmethyl-carbamic acid tert-butyl ester (**548**, 0.397 g, 0.57 mmol, prepared according to the protocol of Scheme 159, Example 5, replacing 4-(aminomethyl)pyridine **516** with 4-fluoro-benzylamine in step 1, isolated after step 3), triethylsilane (1.0 mL, 6.3 mmol), and trifluoroacetic acid (0.5 mL, 6 mmol) in acetonitrile (10 mL) was stirred at 40 °C for 2 hours. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with sodium bicarbonate and brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide the desired compound as a yellow solid (**549**, 0.11 g, 9%). MS (ESI) $[M\text{-}H^+]^+ = 451.10$.

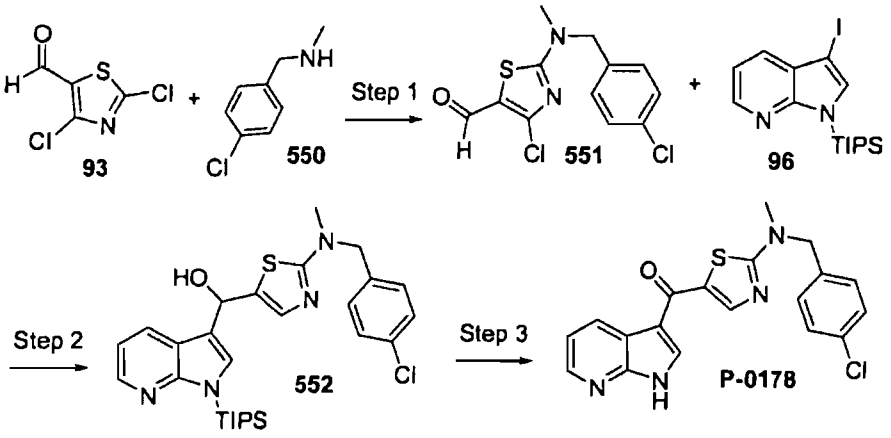
Step 2 – Preparation of [2-(4-fluoro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0177):

[0191] To a solution of (4-fluoro-benzyl)-[5-(1H-pyrrolo[2, 3-b]pyridine-3-carbonyl)-thiazol-2-yl]-carbamic acid tert-butyl ester (**549**, 0.11g, 0.2 mmol) in dichloromethane (2 mL) was added hydrogen chloride (4 M in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into cold sodium bicarbonate solution, extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. After removal of solvents, the residue was washed with ethyl acetate to provide the desired compound as a yellow solid (**P-0177**, 9 mg, 10%). MS (ESI) $[M+H^+]^+ = 353.12$.

Example 20: Synthesis of {2-[(4-chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-0178.

[0192] {2-[(4-Chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0178** was synthesized in 3 steps as shown in Scheme 174.

Scheme 174



Step 1 – Preparation of 4-chloro-2-[(4-chloro-benzyl)-methy l-amino]-thiazole-5-carbaldehyde (551):

[0193] To a solution of (4-chloro-benzyl)-methyl-amine (**550**, 2 g, 0.01 mol) and N,N-diisopropylethylamine (4 mL, 0.03 mol) in tetrahydrofuran (50 mL) was added 2,4-dichloro-thiazole-5-carbaldehyde (**93**, **3** g, 0.01 mmmol) in tetrahydrofuran (20 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was collected by filtration and washed with hexanes to provide the desired compound as a light-yellow solid (**551**, 3.6 g, 90%).

Step 2 – Preparation of {4-chloro-2-[(4-chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (552):

[0194] To a solution of 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**96**, 0.82 g, 2.0 mmol) in tetrahydrofuran (5 mL) at -20 °C, isopropylmagnesium chloride (2 M in tetrahydrofuran, 1.1 mL, 2.2 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C in 10 minutes. The reaction mixture was then cooled to -40 °C. To the reaction mixture was added a solution of 4-chloro-2-[(4-chloro-benzyl)-methyl-amino]-thiazole-5-carbaldehyde (**551**, 0.41 g, 1.4 mmol) in tetrahydrofuran (10 mL). The reaction mixture was allowed to warm to -10 °C in 30 minutes. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexanes to provide the desired compound as a yellow solid (**552**, 0.5 g, 60%). MS (ESI) $[M+H^+]^+ = 575.29$.

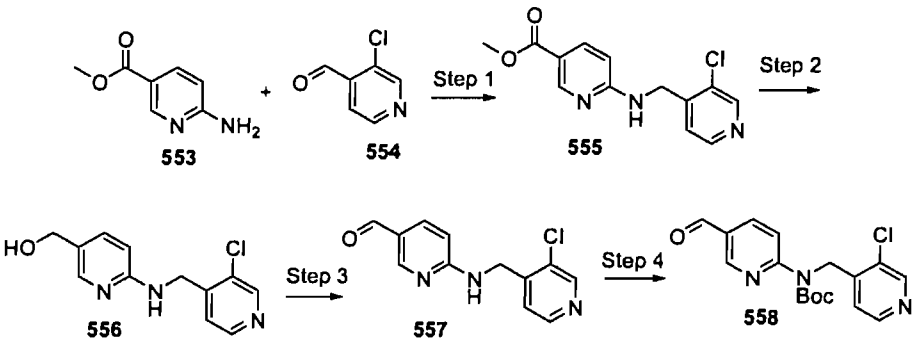
*Step 3 – Preparation of {2-[(4-chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-0178**):*

[0195] A mixture of {4-chloro-2-[(4-chloro-benzyl)-methyl-amino]-thiazol-5-yl}-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**552**, 1 g, 2 mmol), triethylsilane (2 mL, 12 mmol), and trifluoroacetic acid (1 mL, 13 mmol) in acetonitrile (10 mL) was stirred at 40 °C for 2 hours. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with sodium bicarbonate and brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide the desired compound as a yellow solid (**P-0178**, 0.17 g, 30%). MS (ESI) $[M+H^+]^+ = 383.09$.

Example 21: Synthesis of aldehyde intermediates.

[0196] (3-Chloro-pyridin-4-ylmethyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **558** was synthesized in 4 steps from 6-amino-nicotinic acid methyl ester **553** as shown in Scheme 175.

Scheme 175



Step 1 – Synthesis of 6-[(3-chloro-pyridin-4-ylmethyl)-amino]-nicotinic acid methyl ester (555):

[0197] To 6-amino-nicotinic acid methyl ester (**553**, 2.15 g, 0.014 mol) in acetonitrile (60.0 mL) were added 3-chloro-pyridine-4-carbaldehyde (**554**, 2.00 g, 0.014 mol), triethylsilane (11.00 mL, 0.069 mol) and trifluoroacetic acid (5.00 mL, 0.065 mol). The reaction was stirred at 80 °C overnight. The reaction was concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**555**, 1.5 g, 38.2%). MS (ESI) $[M+H^+]^+ = 278.9$.

Step 2 – Synthesis of 6-[(3-Chloro-pyridin-4-ylmethyl)-amino]-pyridin-3-yl-methanol (556):

[0198] To 6-[(3-chloro-pyridin-4-ylmethyl)-amino]-nicotinic acid methyl ester (**555**, 1.00 g, 3.60 mmol) in tetrahydrofuran (120 mL) was added a solution of lithium tetrahydroaluminate (1.00 M in tetrahydrofuran, 5.00 mL) under an atmosphere of nitrogen at room temperature. The reaction

was stirred at room temperature overnight, followed with addition of sodium sulfate decahydrate. After 1 hour, the reaction mixture was filtered, concentrated, and purified with silica gel column chromatography eluting with 2% to 20% methanol in dichloromethane to give the desired compound as a white solid (**556**, 0.5 g, 56%). MS (ESI) $[M+H^+]^+ = 250.1$.

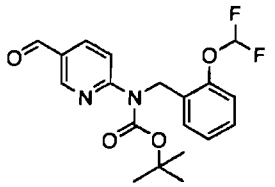
Step 3 – Synthesis of 6-[(3-chloro-pyridin-4-ylmethyl)-amino]-pyridine-3-carbaldehyde (557):

[0199] To 6-[(3-chloro-pyridin-4-ylmethyl)-amino]-pyridin-3-yl-methanol (**556**, 0.50 g, 2.00 mmol) in tetrahydrofuran (20.0 mL) was added Dess-Martin periodinane (1.02 g, 2.40 mmol). The reaction was stirred at room temperature for 10 minutes, then poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give crude compound (**557**, 0.45 g, 91%) that was used in the next step without further purification.

Step 4 – Synthesis of (3-chloro-pyridin-4-ylmethyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (558):

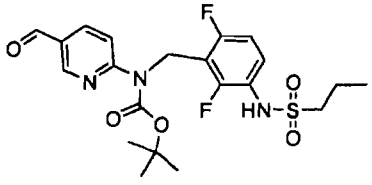
[0200] To 6-[(3-chloro-pyridin-4-ylmethyl)-amino]-pyridine-3-carbaldehyde (**557**, 0.45 g, 1.80 mmol) in dichloromethane (20.0 mL) were added di-tert-butyldicarbonate (0.65 g, 3.00mmol), 4-dimethylaminopyridine (0.012 g, 0.010 mmol) and triethylamine (0.28 mL, 2.00 mmol). The reaction was stirred at room temperature overnight, then concentrated and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**558**, 250 mg, 40.0%).

[0201] (2-Difluoromethoxy-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **559**



was prepared following the protocol of Scheme 175, substituting 3-chloro-pyridine-4-carbaldehyde **554** with 2-difluoromethoxy-benzaldehyde in Step 1.

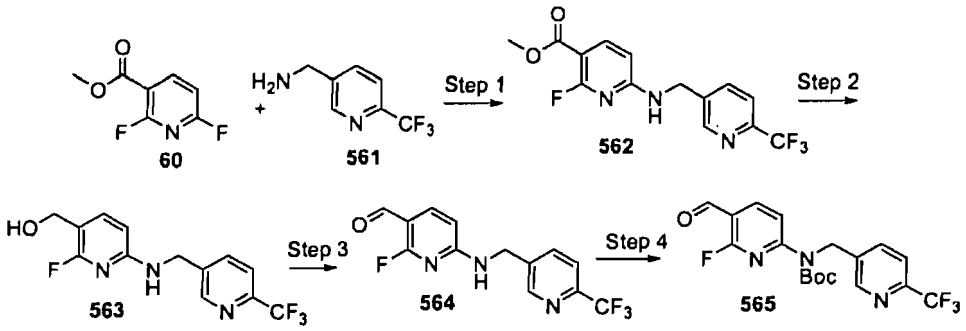
[0202] [2,6-Difluoro-3-(propane-1-sulfonylamino)-benzyl]-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **560**



was prepared following the protocol of Scheme 175, substituting 3-chloro-pyridine-4-carbaldehyde **554** with propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide in Step 1. MS (ESI) $[M+H^+]^+ = 470.3$.

[0203] (6-Fluoro-5-formyl-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **565** was synthesized in 4 steps from 2,6-Difluoro-nicotinic acid methyl ester **60** as shown in Scheme 176.

Scheme 176



Step 1 – Synthesis of 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-nicotinic acid methyl ester (562):

[0204] To 2,6-difluoro-nicotinic acid methyl ester (**60**, 1.82 g, 0.0105 mol) in N,N-dimethylformamide (20.0 mL), under an atmosphere of nitrogen at -40 °C, C-(6-trifluoromethyl-pyridin-3-yl)-methylamine (**561**, 1.00 g, 5.68 mmol) was added. The reaction was stirred at -40 °C, then allowed to warm to room temperature for 2 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 35% to 100% ethyl acetate in hexane to give a white solid (**562**, 1.40 g, 74.9). MS (ESI) $[M+H^+]^+ = 330.1$.

Step 2 – Synthesis of 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-yl-methanol (563):

[0205] To 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-nicotinic acid methyl ester (**562**, 1.40 g, 4.25 mmol) in tetrahydrofuran (100.0 mL) under an atmosphere of nitrogen at room temperature, a solution of lithium tetrahydroaluminate (1.00 M in tetrahydrofuran, 10.0 mL) was added slowly. The reaction was stirred at room temperature overnight, followed by addition of an appropriate amount of sodium sulfate decahydrate. After 1 hour, the reaction mixture was filtered and concentrated to give crude compound (**563**, 1.2 g, 93.7%) that was used in the next step without further purification.

Step 3 – Synthesis of 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridine-3-carbaldehyde (564):

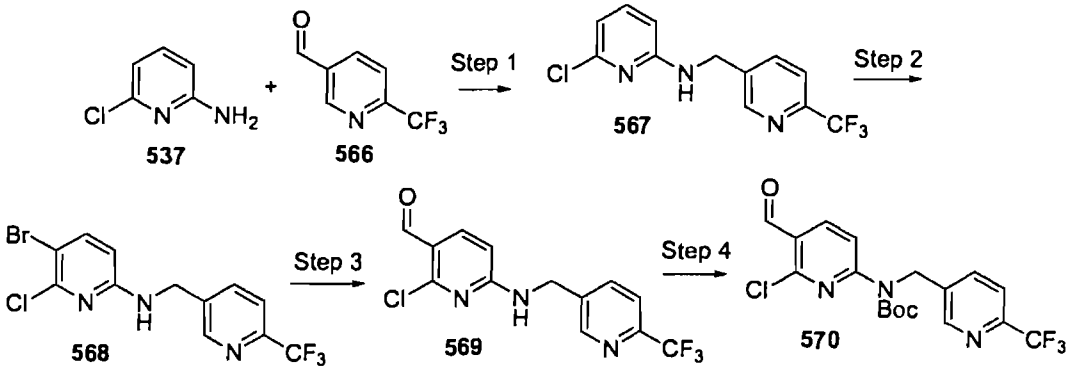
[0206] To 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridin-3-yl-methanol (**563**, 1.20 g, 3.98 mmol) in dichloromethane (40.0 mL) was added Dess-Martin periodinane (1.86 g, 4.38 mmol). The reaction was stirred at room temperature for 10 minutes, then poured into aqueous sodium thiosulfate and potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**564**, 0.28 g, 23.5%).

Step 4 – Synthesis of (6-fluoro-5-formyl-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (565):

[0207] To 2-fluoro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridine-3-carbaldehyde (**564**, 0.28 g, 0.94 mmol) in tetrahydrofuran (10.0 mL) were added di-tert-butyldicarbonate (0.245 g, 1.12 mmol) and 4-dimethylaminopyridine (0.050 g, 0.41 mmol). The reaction was stirred at room temperature overnight, then concentrated and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**565**, 0.22 g, 59%).

[0208] (6-Chloro-5-formyl-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **570** was synthesized in 4 steps from 6-chloro-pyridin-2-ylamine **537** as shown in Scheme 177.

Scheme 177



Step 1 – Synthesis of (6-chloro-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (567):

[0209] To 6-chloro-pyridin-2-ylamine (**537**, 0.760 g, 5.91 mmol) in acetonitrile (30.0 mL), 6-trifluoromethyl-pyridine-3-carbaldehyde (**566**, 1.06 g, 6.05 mmol), trifluoroacetic acid (3.00 mL,

0.0389 mol) and triethylsilane (6.00 mL, 0.0376 mol) were added. The reaction was heated to reflux for 4 hours. The reaction was concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated and purified with silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**567**, 1.60 g, 94.1%).

Step 2 – Synthesis of (5-bromo-6-chloro-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (568):

[0210] To (6-chloro-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**567**, 4.50 g, 0.0156 mol) in acetonitrile (120.0 mL) under an atmosphere of nitrogen, N-bromosuccinimide (3.03 g, 0.0170 mol) in acetonitrile (50 mL) was added slowly. The reaction was stirred at room temperature overnight, then poured into water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, concentrated and purified with silica gel column chromatography eluting with 25% to 100% ethyl acetate in hexane to give a white solid (**568**, 6.20 g, 80.2%).

Step 3 – Synthesis of 2-chloro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridine-3-carbaldehyde (569):

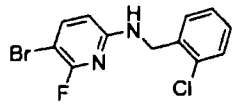
[0211] To (5-bromo-6-chloro-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**568**, 4.60 g, 0.0125 mol) in tetrahydrofuran (60.0 mL) under an atmosphere of nitrogen at -78 °C, isopropylmagnesium chloride (2.00 M in tetrahydrofuran, 6.44 mL) was added over 10 minutes. The reaction was stirred at -78 °C for 20 minutes, and then allowed to warm to room temperature for 10 minutes. The reaction was cooled to -78 °C, followed by adding tert-butyllithium (1.70 M in hexane, 15.3 mL) over 10 minutes. After 40 minutes, N,N-dimethylformamide (1.23 mL, 0.0158 mol) was added and the reaction was stirred at -78 °C for 40 minutes, then allowed to warm to room temperature for 30 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 35% to 100% ethyl acetate in hexane to give a light yellow solid (**569**, 2.84 g, 71.7%).

Step 4 – Synthesis of (6-chloro-5-formyl-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (570)

[0212] To a solution of 2-chloro-6-[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-pyridine-3-carbaldehyde (**569**, 0.545 g, 1.73 mmol) in tetrahydrofuran (10 mL), N,N-diisopropylethylamine (0.60 mL, 3.40 mmol), 4-dimethylaminopyridine (20 mg, 0.10 mmol), and a solution of di-tert-butyldicarbonate (0.41 g, 0.0019 mol) were added. The reaction mixture was stirred at room temperature overnight, then concentrated, poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica

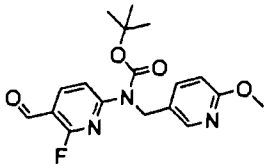
gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**570**, 0.60 g, 83.6%).

[0213] (5-Bromo-6-fluoro-pyridin-2-yl)-(2-chloro-benzyl)-amine **571**



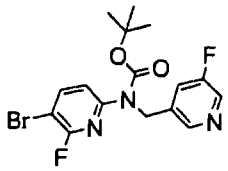
was prepared following the protocol of Steps 1 and 2 of Scheme 177, substituting 6-chloro-pyridin-2-ylamine **537** and 6-trifluoromethyl-pyridine-3-carbaldehyde **566** with 6-fluoro-pyridin-2-ylamine and 2-chloro-benzaldehyde, respectively in Step 1.

[0214] (6-Fluoro-5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **572**



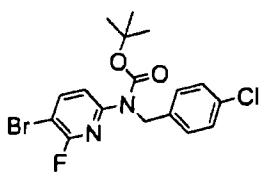
was prepared following the protocol of Scheme 177, substituting 6-chloro-pyridin-2-ylamine **537** and 6-trifluoromethyl-pyridine-3-carbaldehyde **566** with 6-fluoro-pyridin-2-ylamine and 6-methoxy-pyridine-3-carbaldehyde, respectively in Step 1.

[0215] (5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **631**



was prepared following the protocol of Scheme 177, substituting 6-chloro-pyridin-2-ylamine **537** and 6-trifluoromethyl-pyridine-3-carbaldehyde **566** with 6-fluoro-pyridin-2-ylamine and 5-fluoro-pyridine-3-carbaldehyde, respectively in Step 1, without Step 3 (i.e. the product of Step 2 is reacted according to Step 4).

[0216] (5-Bromo-6-fluoro-pyridin-2-yl)-(4-chloro-benzyl)-carbamic acid tert-butyl ester **637**

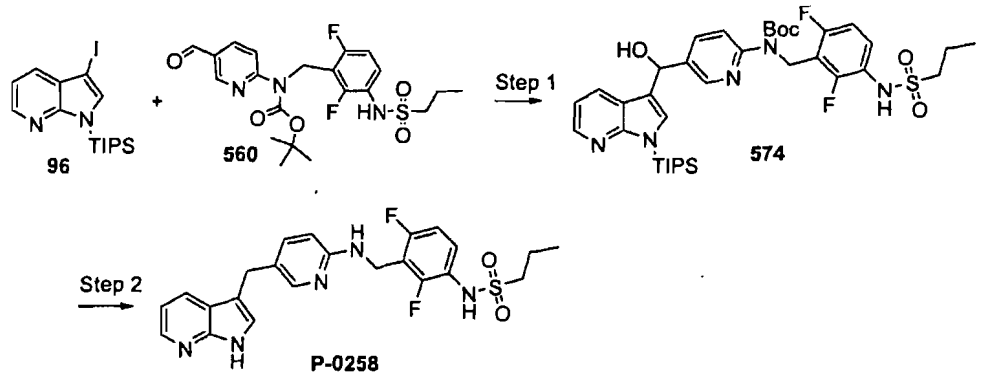


was prepared following the protocol of Scheme 177, substituting 6-chloro-pyridin-2-ylamine **537** and 6-trifluoromethyl-pyridine-3-carbaldehyde **566** with 6-fluoro-pyridin-2-ylamine and 5-chloro-benzaldehyde, respectively in Step 1, without Step 3 (i.e. the product of Step 2 is reacted according to Step 4).

Example 22: Synthesis of propane-1-sulfonic acid (2,4-difluoro-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl-phenyl)-amide P-0258

[0217] Propane-1-sulfonic acid (2,4-difluoro-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl-phenyl)-amide **P-0258** was synthesized in 2 steps from 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **96** as shown in Scheme 178.

Scheme 178



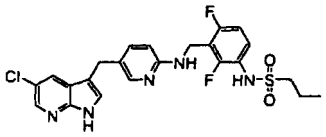
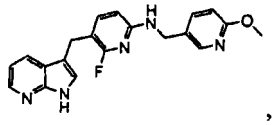
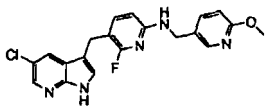
Step 1 – Synthesis of [2,6-difluoro-3-(propane-1-sulfonylamino)-benzyl]-5-[hydroxy-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyr idin-3-yl)-methyl]-pyridin-2-yl-carbamic acid tert-butyl ester (574):

[0218] To a solution of 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**96**, 0.644 g, 1.61 mmol) in tetrahydrofuran (10.0 mL) at -40 °C under nitrogen, isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.80 mL) was added slowly. The reaction was allowed to warm to 15 °C over 100 minutes, then cooled to -40 °C, followed by adding [2,6-difluoro-3-(propane-1-sulfonylamino)-benzyl]-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**560**, 0.100 g, 0.21 mmol, prepared as described in Example 21, Scheme 175) in tetrahydrofuran (2.0 mL). The reaction was allowed to warm to 5 °C over 2 hours, then poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a yellow solid (**574**, 75 mg, 47%). MS (ESI) $[M+H^+]^+ = 744.7$.

Step 2 – Synthesis of Propane-1-sulfonic acid (2,4-difluoro-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl-phenyl)-amide (P-0258):

[0219] To [2,6-difluoro-3-(propane-1-sulfonylamino)-benzyl]-5-[hydroxy-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyr idin-3-yl)-methyl]-pyridin-2-yl-carbamic acid tert-butyl ester (**574**, 75.0 mg, 0.10 mmol) in acetonitrile (10.0 mL) were added triethylsilane (0.40 mL, 2.5 mmol) and trifluoroacetic acid (0.20 mL, 2.6 mmol). The reaction was stirred at 80 °C for 4 hours. The reaction was poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 15% methanol in dichloromethane to give an off-white solid (**P-0258**, 29.3 mg, 61.6%). MS (ESI) $[M+H^+]^+ = 472.4$.

[0220] Propane-1-sulfonic acid (3-{[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-2,4-difluoro-phenyl)-amide (**P-0259**), [6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-0378**), and [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-0379**),

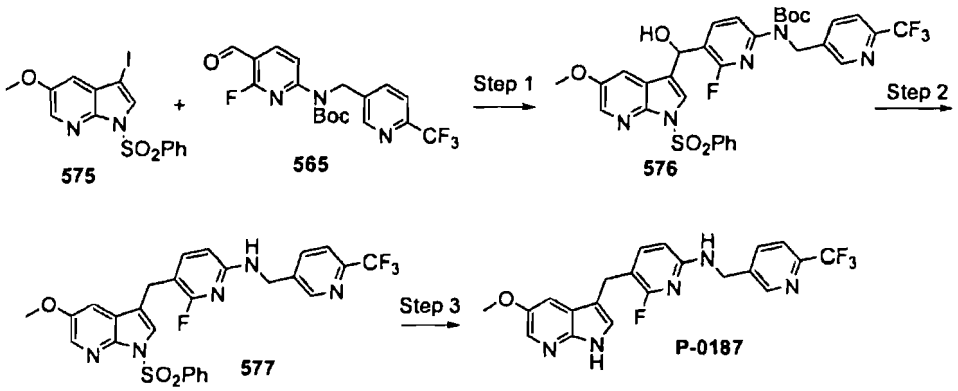

, 
, and 
,

respectively, were prepared following the protocol of Scheme 178. **P-0259** was prepared by replacing 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **96** with 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine in Step 1 (MS $[M+H^+]^+ = 506.1$). **P-0378** was prepared by replacing [2,6-difluoro-3-(propane-1-sulfonylamino)-benzyl]-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **560** with (6-Fluoro-5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **572** (prepared as described in Example 21, Scheme 177) in Step 1 (MS $[M+H^+]^+ = 364.1$). **P-0379** was prepared by replacing both azaindole **96** with 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine and aldehyde **560** with aldehyde **572** in Step 1 (MS $[M+H^+]^+ = 400.0$).

Example 23: Synthesis of [6-fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine P-0187

[0221] [6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0187** was synthesized in 3 steps from 1-benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine **575** as shown in Scheme 179.

Scheme 179



Step 1 - Synthesis of 5-[(1-benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (576):

[0222] To 1-benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine (**575**, 0.326 g, 0.000788 mol) in tetrahydrofuran (3.00 mL) at -45 °C under nitrogen, isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.380 mL) was added slowly. The reaction was allowed to warm to -25 °C in 30 minutes, and then cooled to -45 °C followed by adding (6-fluoro-5-formyl-pyridin-2-yl)-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**565**, 80.0 mg, 0.20 mmol, prepared as described in Example 21, Scheme 176) in tetrahydrofuran (1.0 mL). The reaction was allowed to warm to room temperature over 2 hours. The reaction was poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**576**, 0.080 g, 60%). MS (ESI) $[M+H^+]^+ = 688.1$.

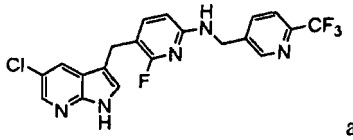
Step 2 – Synthesis of [5-(1-Benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (577):

[0223] To 5-[(1-benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-6-fluoro-pyridin-2-yl-(6-trifluoromethyl-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**576**, 0.100 g, 0.15 mmol) in acetonitrile (12.6 mL) were added triethylsilane (0.34 mL, 2.10 mmol) and trifluoroacetic acid (0.17 mL, 2.20 mmol). The reaction was heated to 80 °C for 2 hours. The reaction was poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give the crude compound (**577**, 90 mg, 100%) that was used in the next step without further purification.

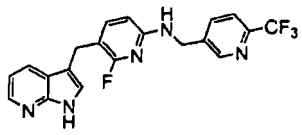
*Step 3 – Synthesis of [6-Fluoro-5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0187**):*

[0224] To [5-(1-benzenesulfonyl-5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**577**, 0.08 g, 0.13 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.110 g, 0.35 mmol). The reaction was stirred at room temperature overnight, then poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give an off-white solid (**P-0187**, 8.1 mg, 10%). MS (ESI) $[M+H^+]^+$ = 431.9.

[0225] [6-Fluoro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0186** and [6-Fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine **P-0188**,



and



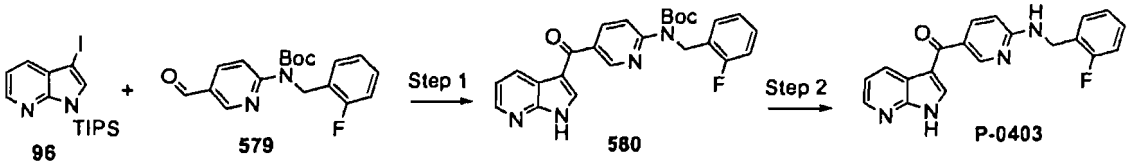
respectively,

were prepared following the protocol of Scheme 179, substituting 1-benzenesulfonyl-3-iodo-5-methoxy-1H-pyrrolo[2,3-b]pyridine **575** with 1-benzenesulfonyl-3-iodo-5-chloro-1H-pyrrolo[2,3-b]pyridine or 1-Benzenesulfonyl-3-iodo-1H-pyrrolo[2,3-b]pyridine, respectively, in Step 1. MS (ESI) $[M+H^+]^+$ = 435.7 and 401.6, respectively.

Example 24: Synthesis of [6-(2-fluoro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-0403

[0226] Synthesis of [6-(2-fluoro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0403** was synthesized in 2 steps from 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **96** as shown in Scheme 180.

Scheme 180



Step 1 – (2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-carbamic

acid tert-butyl ester (580):

[0227] To 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**96**, 0.550 g, 1.37 mmol) in tetrahydrofuran (15.0 mL) at -40 °C under nitrogen, isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.65 mL) was added slowly. The reaction was allowed to warm to 5 °C over 70 minutes, then cooled to -40 °C, followed by adding (2-fluoro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**579**, prepared according to the protocol of Example 1, Scheme 19, Steps 1-3, replacing 4-chlorobenzaldehyde **40** with 2-fluoro-benzaldehyde in Step 1) in tetrahydrofuran (4.0 mL). The reaction was allowed to warm to room temperature over 1 hour, then poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**580**, 0.14 g, 26%). MS (ESI) $[M+H^+]^+ = 447.0$.

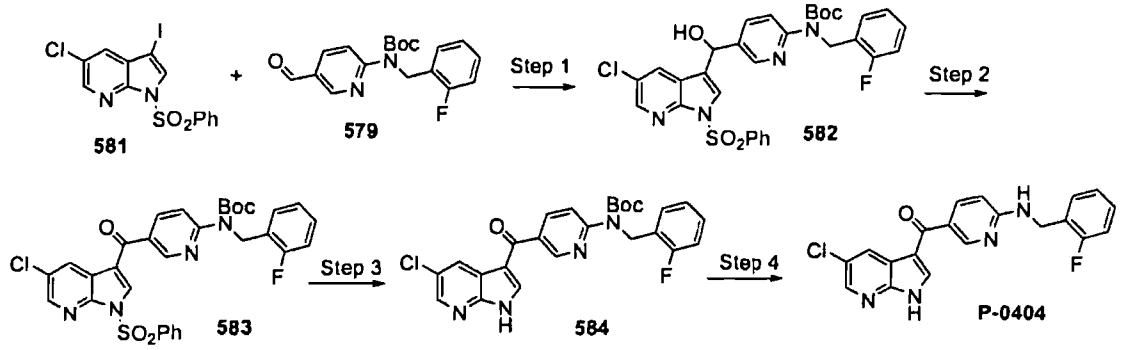
Step 2 - Synthesis of [6-(2-Fluoro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0403):

[0228] To (2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-carbamic acid tert-butyl ester (**580**, 0.080 g, 0.18 mmol) in dichloromethane (3.0 mL) was added trifluoroacetic acid (1.0 mL, 0.013 mol). The reaction was stirred at room temperature overnight, then concentrated, poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 15 % methanol in dichloromethane to give the desired compound (**P-0403**, 15.0 mg, 23.0%). MS (ESI) $[M+H^+]^+ = 347.5$.

Example 25: Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(2-fluoro-benzylamino)-pyridin-3-yl]-methanone P-0404

[0229] (5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(2-fluoro-benzylamino)-pyridin-3-yl]-methanone **P-0404** was synthesized in 4 steps from 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **581** as shown in Scheme 181.

Scheme 181



Step 1 – Synthesis of 5-[(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl-(2-fluoro-benzyl)-carbamic acid tert-butyl ester (582)

[0230] To a solution of 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**581**, 0.420 g, 1.00 mmol) in tetrahydrofuran (15.0 mL) at -40 °C under nitrogen, isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.49 mL) was added slowly. The reaction was allowed to warm to 5 °C over 70 minutes, then cooled to -40 °C, followed by adding (2-fluoro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **579** in tetrahydrofuran (6.0 mL). The reaction was allowed to warm to room temperature over 1 hour, then poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**582**, 0.25 g, 41%). MS (ESI) $[M+H^+]^+ = 623.1$.

Step 2 – Synthesis of [5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-(2-fluoro-benzyl)-carbamic acid tert-butyl ester (583):

[0231] To 5-[(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl-(2-fluoro-benzyl)-carbamic acid tert-butyl ester (**582**, 0.25 g, 0.40 mmol) in dichloromethane (5.0 mL) was added Dess-Martin periodinane (0.20 g, 0.48 mmol). The reaction was stirred at room temperature for 10 minutes, then poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**583**, 0.060 g., 24%).

Step 3 – Synthesis of [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-(2-fluoro-benzyl)-carbamic acid tert-butyl ester (584):

[0232] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-

(2-fluoro-benzyl)-carbamic acid tert-butyl ester (**583**, 60.0 mg, 0.097 mmol) in tetrahydrofuran (1.0 mL) was added aqueous potassium carbonate (1.0 M, 1.0 mL). The reaction was irradiated with microwave on 300 watts, 100°C for 10 minutes, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give crude compound (**584**, 0.040 g, 64%) that was used in the next step without further purification.

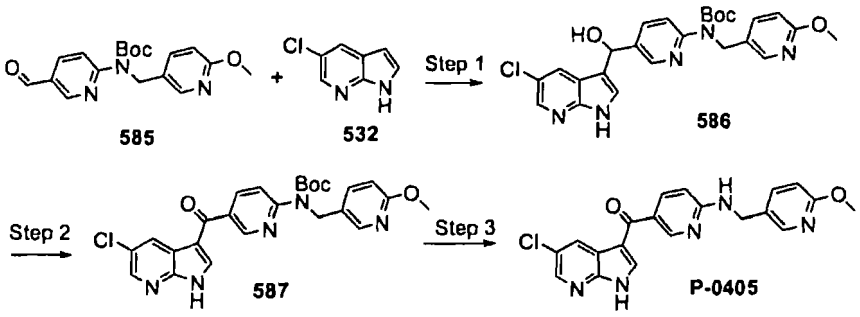
*Step 4 – Synthesis of (5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(2-fluoro-benzylamino)-pyridin-3-yl]-methanone (**P-0404**):*

[0233] To [5-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-(2-fluoro-benzyl)-carbamic acid tert-butyl ester (**584**, 0.030 g, 0.062 mmol) in dichloromethane (1.0 mL) was added trifluoroacetic acid (1.0 mL, 0.013 mol). The reaction was stirred at room temperature overnight, then poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 15% methanol in dichloromethane to give the desired compound (**P-0404**, 2.8 mg, 12%). MS (ESI) $[M+H^+]^+ = 381.0$.

Example 26: Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-yl-methanone P-0405

[0234] (5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-yl-methanone **P-0405** was synthesized in 3 steps from 5-Chloro-1H-pyrrolo[2,3-b]pyridine **532** as shown in Scheme 182.

Scheme 182



Step 1 – Synthesis of 5-[(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (586):

[0235] To 5-chloro-1H-pyrrolo[2,3-b]pyridine (**532**, 0.092 g, 0.60 mmol) in methanol (15.0 mL) were added (5-formyl-pyridin-2-yl)-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester

(**585**, 0.240 g, 0.70 mmol, prepared according to the protocol of Example 1, Scheme 19, Steps 1-3, replacing 4-chlorobenzaldehyde **40** with 6-methoxy-pyridine-3-carbaldehyde in Step 1) and potassium hydroxide (1.2 g, 0.021 mol). The reaction was stirred at room temperature overnight, then poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**586**, 0.110 g, 37%).

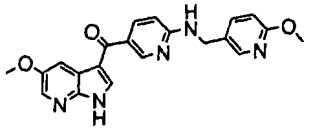
Step 2 – Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (587):

[0236] To 5-[(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**586**, 0.060 g, 0.12 mmol) in dichloromethane (10.0 mL) was added Dess-Martin periodinane (0.062 g, 0.15 mmol). The reaction was stirred at room temperature for 10 minutes. The reaction was concentrated and purified with a silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**587**, 0.020 g, 33%).

Step 3 – Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-[(6-methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-yl-methanone (P-0405):

[0237] To [5-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**587**, 0.020 g, 0.040 mmol) in dichloromethane (2.0 mL) was added trifluoroacetic acid (0.30 mL, 0.0039 mol). The reaction was stirred at room temperature for 2 hours, then poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**P-0405**, 5.5 mg, 34%). MS (ESI) $[M+H^+]^+$ = 394.3.

[0238] {6-[(6-Methoxy-pyridin-3-ylmethyl)-amino]-pyridin-3-yl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0406**

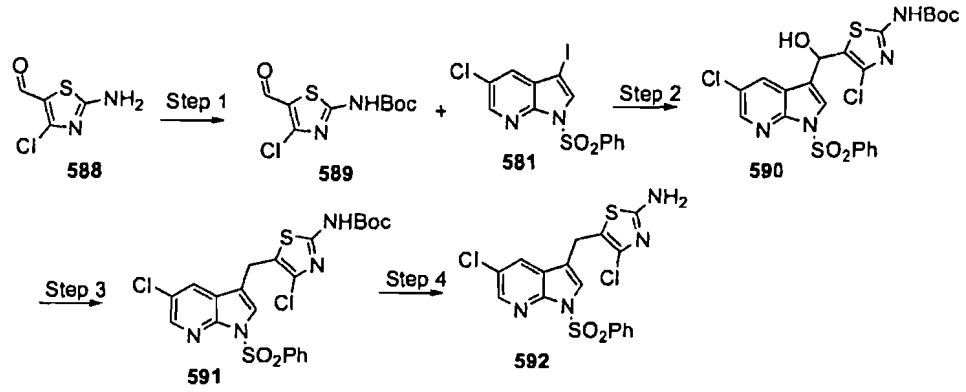


was prepared following the protocol of Scheme 182, substituting 5-chloro-1H-pyrrolo[2,3-b]pyridine **532** with 5-methoxy-1H-pyrrolo[2,3-b]pyridine in step 1. MS (ESI) $[M+H^+]^+$ = 390.1.

Example 27: Synthesis of intermediate 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine 592

[0239] 5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **592** was synthesized in 4 steps from 2-amino-4-chloro-thiazole-5-carbaldehyde **588** as shown in Scheme 183.

Scheme 183



Step 1 – Synthesis of (4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (589):

[0240] To 2-amino-4-chloro-thiazole-5-carbaldehyde (**588**, 5.00 g, 0.0308 mol) in tetrahydrofuran (122 mL) were added di-tert-butyldicarbonate (7.38 g, 0.0338 mol) and 4-dimethylaminopyridine (0.35 g, 0.0029 mol). The reaction was stirred at 58 °C for 2 hours, then concentrated and purified with silica gel column chromatography eluting with 20% to 80% ethyl acetate in hexane to give a yellow solid (**589**, 7.0 g, 87%).

Step 2 – Synthesis of 5-[(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-4-chloro-thiazol-2-yl-carbamic acid tert-butyl ester (590):

[0241] To a solution of 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**581**, 4.40 g, 10.5 mmol) in tetrahydrofuran (30.0 mL) at -45 °C under nitrogen, a solution of isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 5.4 mL) was added slowly over 10 minutes. The reaction was allowed to warm to -25 °C over 30 minutes. The reaction was cooled to -65 °C, followed by adding the cold deprotonated (4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester **589**, which was prepared in situ by adding isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 5.0 mL) to (4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (**589**, 2.51 g, 9.55 mmol) in tetrahydrofuran (23.0 mL) at -78 °C under an atmosphere of nitrogen. The reaction was allowed to warm to room temperature in 2 hours, then poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was dried over anhydrous

sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 25%to 100% ethyl acetate in hexane to give the desired compound (**590**, 3.70 g, 60.3%). MS (ESI) $[M+H^+]^+$ = 554.2.

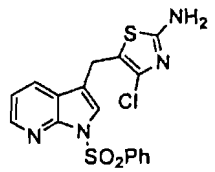
Step 3 – Synthesis of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-carbamic acid tert-butyl ester (591):

[0242] To 5-[(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-4-chloro-thiazol-2-yl-carbamic acid tert-butyl ester (**590**, 0.200 g, 0.32 mmol) in dichloromethane (15.0 mL) were added triethylsilane (0.600 mL, 376 mmol) and trifluoroacetic acid (0.300 mL, 3.89 mmol). The reaction was stirred at room temperature for 3 hours, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 25%to 100% ethyl acetate in hexane to give the desired compound (**591**, 0.155 g, 88.7%). MS (ESI) $[M+H^+]^+$ = 538.9.

Step 4 – Synthesis of 5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine (592):

[0243] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-carbamic acid tert-butyl ester (**591**, 4.30 g, 7.97 mmol) in dichloromethane (70.0 mL) was added a solution of hydrogen chloride (4.00 M in 1,4-dioxane, 42.0 mL). The reaction was stirred at room temperature for 2 days, then concentrated, and titrated with ethyl ether and ethyl acetate to give the desired compound (**592**, 2.60 g, 74.2%). MS (ESI) $[M+H^+]^+$ = 439.0.

[0244] 5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **593**

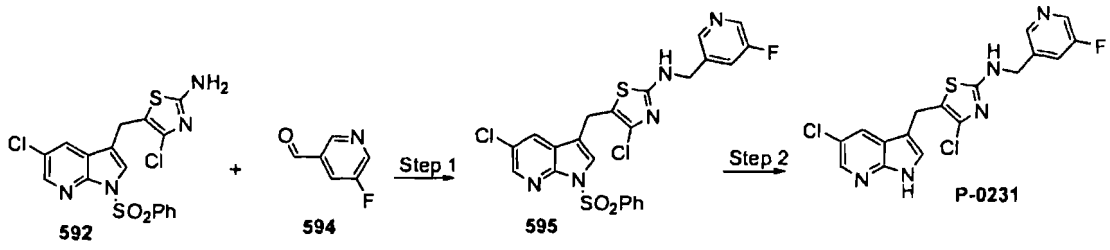


was prepared following the protocol of Scheme 183, substituting 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **581** with 1-benzenesulfonyl-3-iodo-1H-pyrrolo[2,3-b]pyridine in Step 2. MS (ESI) $[M+H^+]^+$ = 404.4.

Example 28: Synthesis of [4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine P-0231

[0245] [4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine **P-0231** was synthesized in 2 steps from 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **592** as shown in Scheme 184.

Scheme 184



Step 1 – Synthesis of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (595):

[0246] To 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine (**592**, 50.0 mg, 0.11 mmol, prepared as described in Example 27, Scheme 183) in ethanol (1.60 mL) and acetic acid (0.08 mL) were added 5-fluoro-pyridine-3-carbaldehyde (**594**, 43 mg, 0.34 mmol) and silica supported cyanoborohydride (1.21 mmol/g, 0.180 g). The reaction was irradiated with microwave on 300 watts, 100°C for 7 minutes. The reaction was poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give the desired compound (**595**, 0.030 g, 48%).

Step 2 – Synthesis of [4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (P-0231):

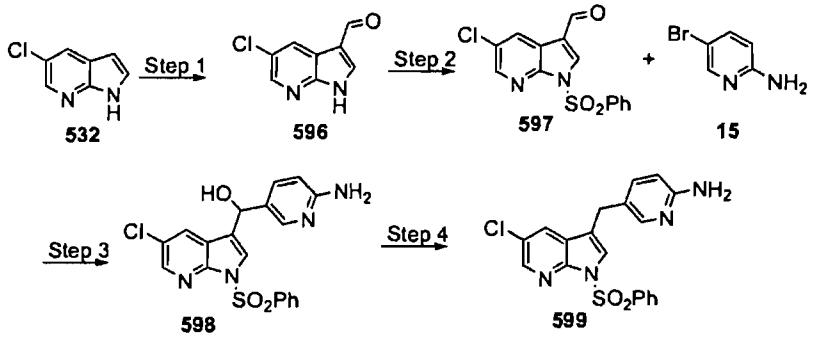
[0247] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**595**, 0.030 g, 0.055 mmol) in tetrahydrofuran (6.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.034 g, 0.11 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 3 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**P-0231**, 1.5 mg,

6.7%). MS (ESI) $[M+H^+]^+ = 408.1$.

Example 29: Synthesis of 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine 599

[0248] 5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **599** was synthesized in 4 steps from 5-chloro-1H-pyrrolo[2,3-b]pyridine **532** as shown in Scheme 185.

Scheme 185



Step 1 – Synthesis of 5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (596):

[0249] To 5-chloro-1H-pyrrolo[2,3-b]pyridine (**532**, 10.0 g, 65.5 mmol) in acetic acid (28.3 mL) were added hexamethylenetetramine (11.9 g, 85.2 mmol) and water (56.7 mL). The reaction was refluxed overnight, followed by addition of 200 mL of water. After 30 minutes, the reaction was filtered to recover the solid, then dried under air to give the desired compound (**596**, 7.0 g. 59%).

Step 2 – Synthesis of 1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (597):

[0250] To 5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**596**, 3.60 g, 0.0199 mol) in dichloromethane (100 mL) were added a solution of potassium hydroxide (9 M in water, 50 mL), tetrabutylammonium hydrogen sulfate (400 mg, 0.001 mol) and benzenesulfonyl chloride (2.9 mL, 0.023 mol). The reaction was stirred at room temperature for 3 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate to give a white solid (**597**, 2.3 g, 36.0%).

Step 3 – Synthesis of (6-amino-pyridin-3-yl)-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (598):

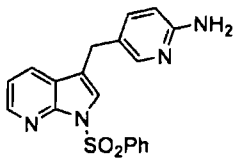
[0251] To 2-amino-5-bromopyridine (**15**, 3.10 g, 17.9 mmol) in tetrahydrofuran (80.0 mL) under

an atmosphere of nitrogen at -78 °C, a solution n-butyllithium (2.50 M in hexane, 7.10 mL) was added slowly. After 30 minutes, 1,2-bis-(chloro-dimethyl-silanyl)-ethane (3.90 g dissolved in tetrahydrofuran 20.0 mL, 18.1 mmol) was added to the reaction mixture slowly, and then allowed to warm to room temperature for 1 hour. The reaction was cooled to -78 °C followed by adding a solution of n-butyllithium (2.50 M in Hexane, 7.10 mL). The reaction mixture was stirred at -78 °C for 30 minutes, then allowed to warm to room temperature for 60 minutes. The reaction mixture was cooled to -78 °C, followed by adding a solution of n-butyllithium (2.50 M in Hexane, 7.50 mL) slowly. After 60 minutes, 1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**597**, 1.90 g in 30 mL tetrahydrofuran, 5.92 mmol) was added to the reaction mixture. The reaction mixture was stirred at -78 °C for 2 hours, then allowed to warm to room temperature for 1 hour. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 20% methanol in dichloromethane to give the desired compound (**598**, 1.25 g, 50.9%). MS (ESI) $[M+H^+]^+ = 415.2$.

Step 4 – Synthesis of 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (599):

[0252] To (6-amino-pyridin-3-yl)-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**598**, 1.00 g, 0.00241 mol) in dichloromethane (25.0 mL) were added triethylsilane (3.00 mL, 0.0188 mol) and trifluoroacetic acid (1.50 mL, 0.0195 mol). The reaction was stirred at room temperature overnight, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**599**, 0.70 g, 73%).

[0253] 5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **600**

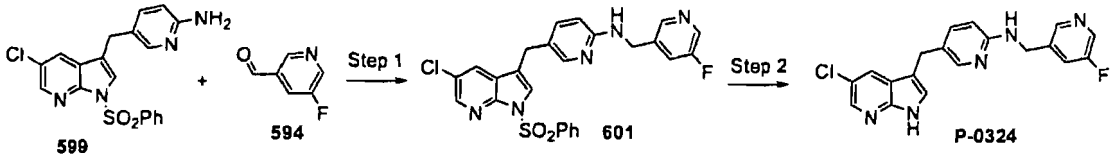


was prepared following the protocol of Scheme 185, substituting 5-chloro-1H-pyrrolo[2,3-b]pyridine **532** with 1H-pyrrolo[2,3-b]pyridine in Step 1. MS (ESI) $[M+H^+]^+ = 365.2$.

Example 30: Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine P-0324

[0254] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine **P-0324** was synthesized in 2 steps from 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **599** as shown in Scheme 186.

Scheme 186



Step 1 – Synthesis of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (601):

[0255] To 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**599**, 80.0 mg, 0.20 mmol, prepared as described in Example 29, Scheme 185) in ethanol (2.0 mL) and acetic acid (0.10 mL, 0.0018 mol) were added 5-fluoro-pyridine-3-carbaldehyde (**594**, 62.7 mg, 0.50 mmol) and sodium cyanoborohydride on silica gel (1.200 mmol/g loading; 0.251 g, 0.30 mmol). The reaction was irradiated with microwave on 300 watts, 100 °C for 10 minutes. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**601**, 0.060 g, 59%).

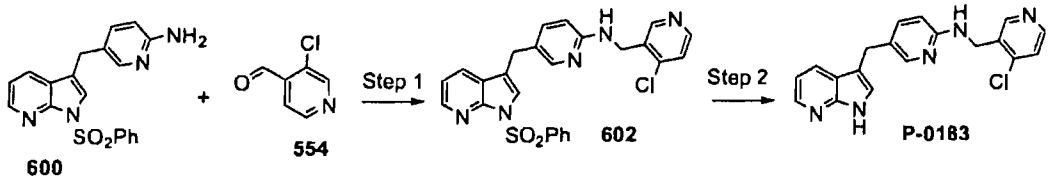
Step 2 – Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (P-0324):

[0256] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine (**601**, 0.060 g, 0.12 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.11 g, 0.35 mmol). The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**P-0324**, 13.5mg, 31%). MS (ESI) $[M+H^+]^+ = 368.0$.

Example 31: Synthesis of (3-Chloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0183

[0257] (3-Chloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0183 was** synthesized in 2 steps from 5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **600** as shown in Scheme 187.

Scheme 187



Step 1 – Synthesis of [5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-pyridin-3-ylmethyl)-amine (602):

[0258] To 5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**600**, 120.0 mg, 0.33 mmol, prepared as described in Example 29, Scheme 185) in acetonitrile (10.0 mL) were added 3-chloro-pyridine-4-carbaldehyde (**554**, 51.3 mg, 0.36 mmol), trifluoroacetic acid (0.30 mL, 0.0039 mol) and triethylsilane (0.60 mL, 0.0038 mol). The reaction was heated to reflux overnight, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 30% to 100% ethyl acetate in hexane to give the desired compound (**602**, 80 mg, 49.6%). MS $[M+H^+]^+ = 490.2$.

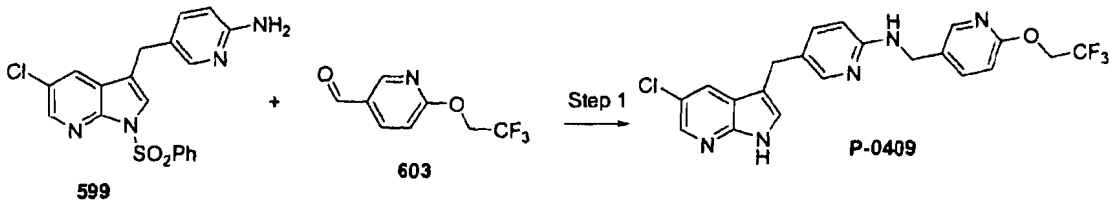
Step 2 – Synthesis of (3-chloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0183):

[0259] To [5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-pyridin-3-ylmethyl)-amine (**602**, 0.08 g, 0.16 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.240 g, 0.76 mmol). The reaction was stirred at room temperature overnight. The reaction was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a yellow solid (**P-0183**, 4.0 mg, 7%). MS (ESI) $[M+H^+]^+ = 350.2$.

Example 32: Synthesis of [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine P-0409

[0260] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine **P-0409** was synthesized in 2 steps from 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **599** as shown in Scheme 188.

Scheme 188



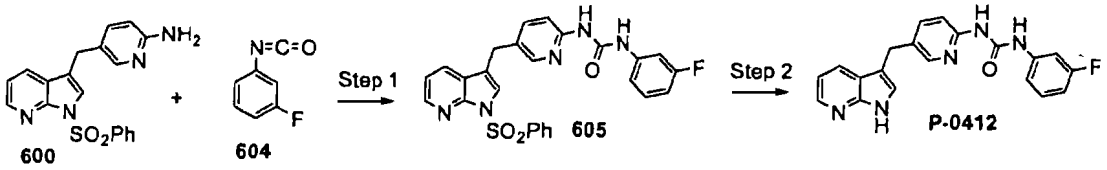
*Step 1 – Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine (**P-0409**):*

[0261] To 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**599**, 124.1 mg, 0.31 mmol, prepared as described in Example 29, Scheme 185) in ethanol (3.00 mL) and acetic acid (0.2 mL) were added 6-(2,2,2-trifluoro-ethoxy)-pyridine-3-carbaldehyde (**603**, 164.0 mg, 0.80 mmol) and silica supported cyanoborohydride (1.21 mmol/g, 0.700 g). The reaction was irradiated with microwave on 300 watts, 100°C for 150 minutes. To the reaction was added a solution of potassium hydroxide (9.0 M in water, 1.0 mL). The reaction was irradiated with microwave on 300 watts, 100 °C for 10 minutes. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**P-0409**, 10.6 mg, 7.6%). MS ESI) $[M+H^+]^+ = 448.4$.

Example 33: Synthesis of 1-(3-fluoro-phenyl)-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-urea P-0412

[0262] 1-(3-Fluoro-phenyl)-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-urea **P-0412** was synthesized in 2 steps from 5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **600** as shown in Scheme 189.

Scheme 189



*Step 1 – Synthesis of 1-[5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-(3-fluoro-phenyl)-urea (**605**):*

[0263] To 5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**600**, 150.0 mg, 0.41 mmol, prepared as described in Example 29, Scheme 185) in acetonitrile (12.5 mL) were added 3-fluoro-isocyanato-benzene (**604**, 61.6 mg, 0.45 mmol), 4-dimethylaminopyridine (10.0 mg, 0.082 mmol) and triethylamine (0.25 mL, 0.0018 mol). The reaction mixture was heated at 70 °C overnight, then poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**605**, 0.100 g, 48.4%).

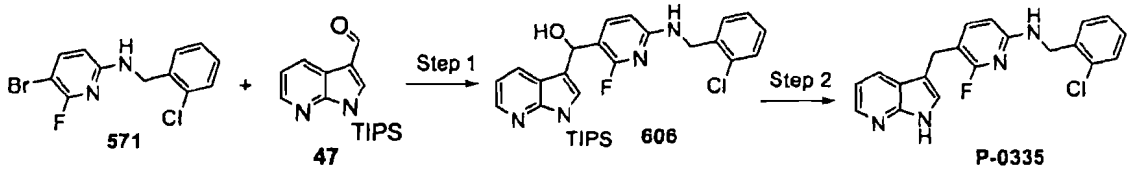
*Step 2 – Synthesis of 1-(3-Fluoro-phenyl)-3-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-urea (**P-0412**):*

[0264] To 1-[5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-3-(3-fluoro-phenyl)-urea (**605**, 0.100 g, 0.20 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.240 g, 0.76 mmol). The reaction was stirred at room temperature for 5 hours, then poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**P-0412**, 17.9 mg, 24.8%). MS (ESI) $[M+H^+]^+$ = 362.2.

Example 34: Synthesis of (2-chloro-benzyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0335

[0265] (2-Chloro-benzyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0335** was synthesized in 2 steps from (5-bromo-6-fluoro-pyridin-2-yl)-(2-chloro-benzyl)-amine **571** as shown in Scheme 190.

Scheme 190



Step 1 – Synthesis of [6-(2-chloro-benzylamino)-2-fluoro-pyridin-3-yl]-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (606):

[0266] To (5-bromo-6-fluoro-pyridin-2-yl)-(2-chloro-benzyl)-amine (**571**, 0.635 g, 2.01 mmol, prepared as described in Example 21, Scheme 177) in tetrahydrofuran (25.0 mL) under an

atmosphere of nitrogen at -78 °C, a solution of n-butyllithium (2.50 M in hexane, 0.80 mL) was added slowly. After 20 minutes, tert-butyllithium (1.7 M in hexane, 2.40 mL) was added to the reaction and after 30 minutes, 1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**47**, 0.575 g, 1.90 mmol) in tetrahydrofuran (8.0 mL) was added to the reaction. The reaction mixture was stirred at -78 °C for 60 minutes, then allowed to warm to room temperature for another 10 minutes. The reaction mixture was poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**606**, 0.180 g, 17.6%). MS (ESI) $[M+H^+]^+ = 539.2$.

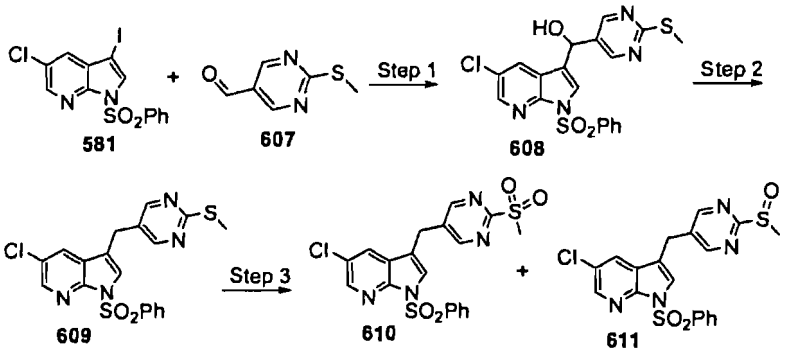
*Step 2 – Synthesis of (2-chloro-benzyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0335**):*

[0267] To [6-(2-chloro-benzylamino)-2-fluoro-pyridin-3-yl]-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**606**, 180.0 mg, 0.33 mmol) in acetonitrile (15.0 mL) were added triethylsilane (1.00 mL, 6.26 mmol) and trifluoroacetic acid (0.50 mL, 6.50 mmol). The reaction was heated to reflux for 2 hours, then poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**P-0335**, 24.9 mg, 19.4%). MS (ESI) $[M+H^+]^+ = 367.0$.

Example 35: Synthesis of 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine 610

[0268] 1-Benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **610** was synthesized in 3 steps from 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **581** as shown in Scheme 191.

Scheme 191



Step 1 – Synthesis of (1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-(2-methylsulfanyl-pyrimidin-5-yl)-methanol (608):

[0269] To a solution of 1-Benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (**581**, 4.36 g, 10.4 mmol) in tetrahydrofuran (100.0 mL) at -40 °C under nitrogen, isopropylmagnesium chloride (2.0 M in tetrahydrofuran. 5.06 mL) was added slowly. The reaction was allowed to warm to 5 °C over 60 minutes, then cooled to -40 °C, followed by adding 2-methylsulfanyl-pyrimidine-5-carbaldehyde (**607**, 1.30 g, 8.43 mmol, dissolved in tetrahydrofuran 15.0 mL). The reaction was allowed to warm to 10 °C over 2 hours. The reaction was poured into aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 15% methanol in dichloromethane to give the desired compound (**608**, 3.00 g, 79.6%). MS (ESI) $[M+H^+]^+ = 447.2$.

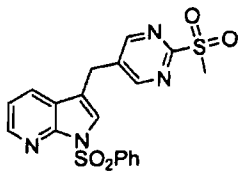
Step 2 – Synthesis of 1-benzenesulfonyl-5-chloro-3-(2-methylsulfanyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (609):

[0270] To (1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-(2-methylsulfanyl-pyrimidin-5-yl)-methanol (**608**, 0.35 g, 0.78 mmol) in dichloromethane (15.0 mL) were added triethylsilane (2.00 mL, 12.52 mmol) and trifluoroacetic acid (1.00 mL, 13.0 mmol). The reaction was stirred at 35 °C overnight, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**609**, 0.25 g, 74%). MS (ESI) $[M+H^+]^+ = 430.9$.

Step 3 - Synthesis of 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (610) and 1-benzenesulfonyl-5-chloro-3-(2-methanesulfinyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (611):

[0271] To 1-benzenesulfonyl-5-chloro-3-(2-methylsulfanyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**609**, 0.500 g, 1.16 mmol) in dichloromethane (15.0 mL) was added meta-chloroperoxybenzoic acid (max. 77%, 0.572 g, 2.55 mmol) at 0 °C. The reaction was stirred at 0 °C for 70 minutes, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compounds (**610**, 0.310 g, 57.7%), MS (ESI) $[M+H^+]^+ = 463.1$; and (**611**, 0.200 g, 38.6%), MS (ESI) $[M+H^+]^+ = 447.2$.

[0272] 1-Benzenesulfonyl-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **612**

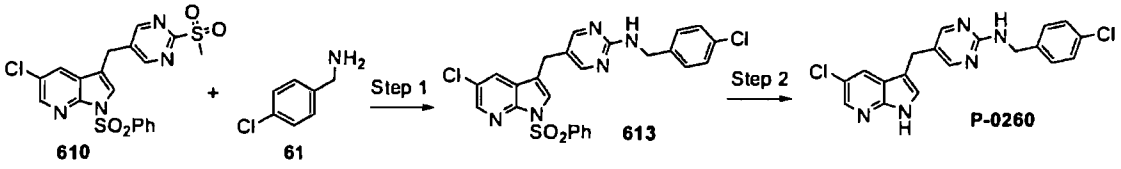


was prepared following the protocol of Scheme 191, substituting 1-benzenesulfonyl-5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **581** with 1-benzenesulfonyl-3-iodo-1H-pyrrolo[2,3-b]pyridine in Step 1.

Example 36: Synthesis of (4-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine P-0260

[0273] (4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **P-0260** was synthesized in 2 steps from 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **610** as shown in Scheme 192.

Scheme 192



Step 1 – Synthesis of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-chloro-benzyl)-amine (613):

[0274] To 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**610**, 0.060 g, 0.13 mmol, prepared as described in Example 35, Scheme 191) in N-methylpyrrolidinone (1.80 mL) was added p-chlorobenzylamine (**61**, 0.20 g, 1.4 mmol). The reaction was irradiated with microwave on 300 watts, 150 °C for 15 minutes, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**613**, 0.05 g, 74%). MS (ESI) $[M+H^+]^+ = 524.3$.

*Step 2 – Synthesis of (4-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0260**):*

[0275] To [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-

yl]-(4-chloro-benzyl)-amine (**613**, 0.050 g, 0.095 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.20 g, 0.63 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight, then poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and washed with ethyl acetate in hexane to give an off-white solid (**P-0260**, 16.9 mg, 46%). MS (ESI) $[M+H^+]^+ = 385.9$.

[0276] Additional compounds were prepared following the protocol of Scheme 192, substituting p-chlorobenzylamine **61** with a suitable amine in Step 1. The following compounds were prepared following this protocol:

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,6-difluoro-benzyl)-amine (**P-0261**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0262**),

(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0263**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-benzyl)-amine (**P-0264**),

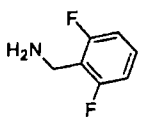
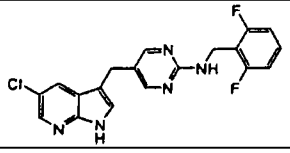
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,4-difluoro-benzyl)-amine (**P-0265**),

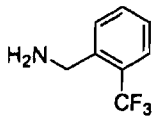
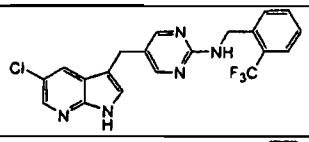
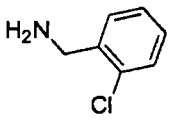
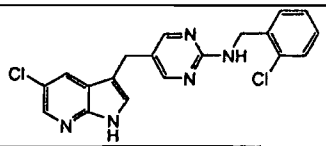
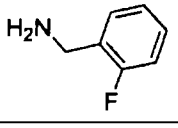
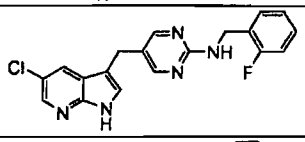
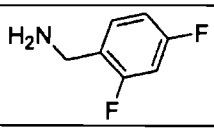
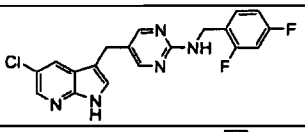
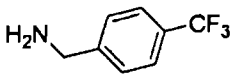
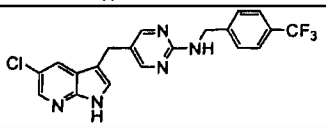
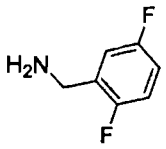
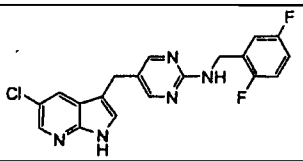
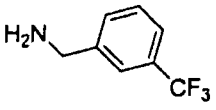
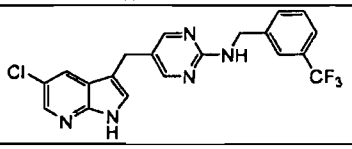
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine (**P-0266**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,5-difluoro-benzyl)-amine (**P-0267**), and

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-trifluoromethyl-benzyl)-amine (**P-0268**).

The following table indicates the amine (Column 2) used in Scheme 192 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

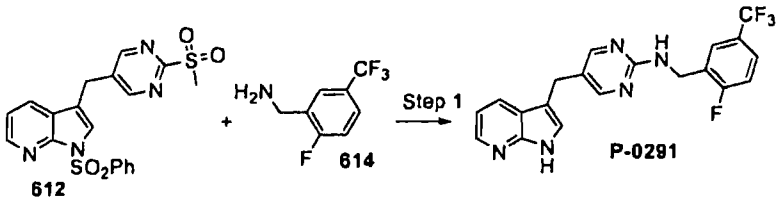
Compound number	Amine in Step 1	Compound	MS (ESI) $[M+H^+]^+$ observed
P-0261			384.1

P-0262			418.9
P-0263			384.2
P-0264			368.2
P-0265			386.2
P-0266			418.9
P-0267			$[M-H^+]^-$ = 384.0
P-0268			419.2

Example 37: Synthesis of (2-fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine P-0291

[0277] (2-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine **P-0291** was synthesized in 1 step from 1-benzenesulfonyl-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine **612** as shown in Scheme 193.

Scheme 193



Step 1 – Synthesis of (2-fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (P-0291):

[0278] To 1-benzenesulfonyl-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**612**, 0.080 g, 0.19 mmol, prepared as described in Example 35, Scheme 191) in N-methylpyrrolidinone (1.00 mL) was added 2-fluoro-5-trifluoromethyl-benzylamine (**614**, 0.20 g, 1.0 mmol). The reaction was irradated with microwave on 300 watts, 150°C for 15 minutes. Potassium hydroxide in water (1.00 M, 2.00 mL) was added to the reaction. The reaction was irradiated with microwave on 300 watts, 90°C for 10 minutes, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**P-0291**, 37.4 mg, 50%). MS (ESI) $[M+H^+]^+$ = 402.6.

[0279] Additional compounds were prepared following the protocol of Scheme 193, substituting 2-fluoro-5-trifluoromethyl-benzylamine **614** with a suitable amine. The following compounds were prepared following this protocol:

(2,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0292**),

(2-Chloro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0293**),

(3-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0294**),

(3,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0295**),

(2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0300**),

(2-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0301**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0302**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethoxy-benzyl)-amine (**P-0303**),

(5-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0304**),

(2,4-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0305**),

(2,4-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0306**),

(4-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0307**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethyl-benzyl)-amine (**P-0308**),

(2-Fluoro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-

amine (**P-0309**),

(2,5-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0310**),

(3-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0311**),

(2-Difluoromethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0312**),

(2,3-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0313**),

(4-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0314**),

(5-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0315**),

(2-Chloro-4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0316**),

(5-Chloro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0317**),

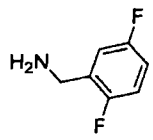
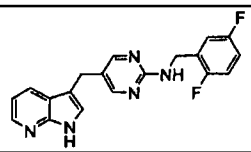
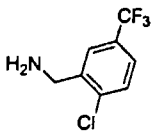
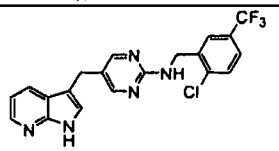
(5-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0318**),

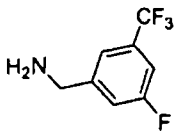
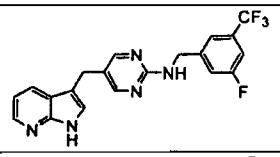
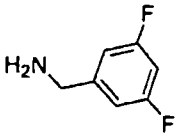
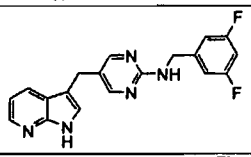
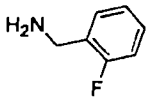
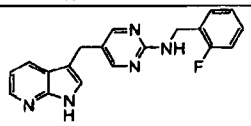
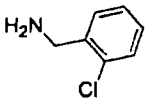
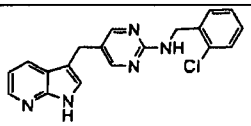
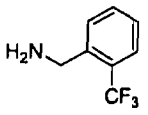
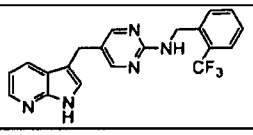
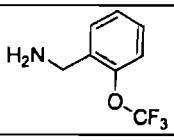
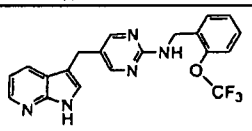
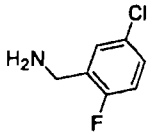
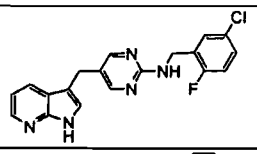
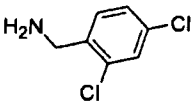
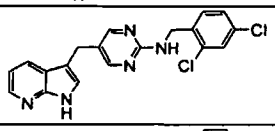
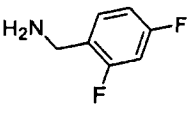
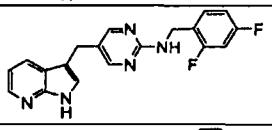
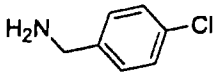
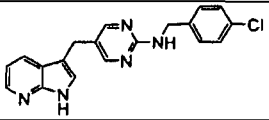
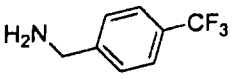
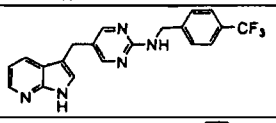
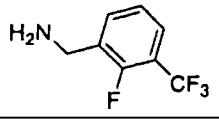
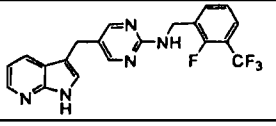
(2-Fluoro-4-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0319**),

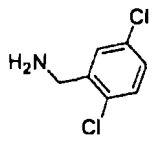
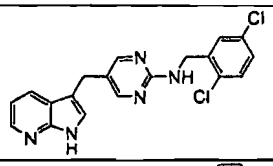
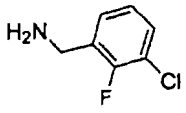
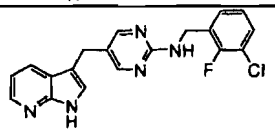
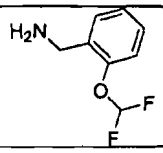
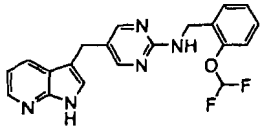
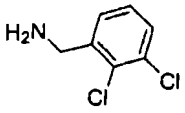
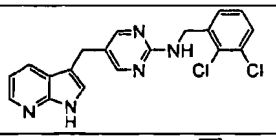
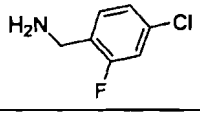
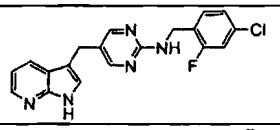
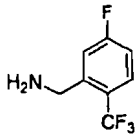
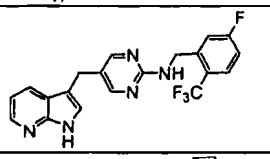
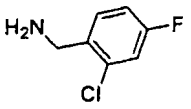
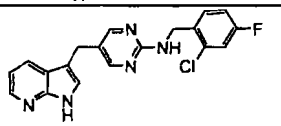
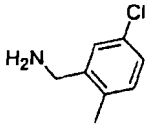
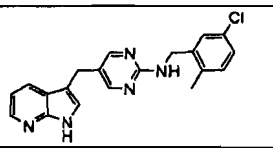
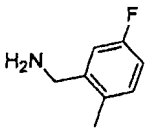
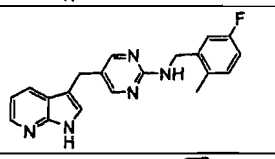
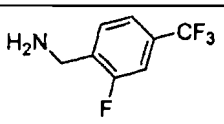
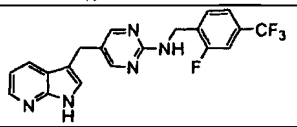
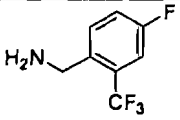
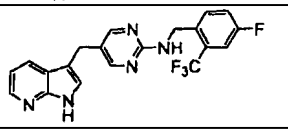
(4-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0320**), and

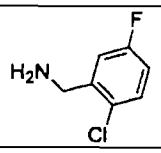
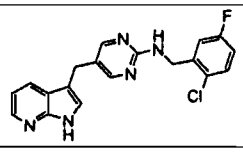
(2-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0407**).

The following table indicates the amine (Column 2) used in Scheme 193 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

Compound number	Amine	Compound	MS (ESI) $[M+H^+]^+$ observed
P-0292			352.3
P-0293			418.2

P-0294			402.5
P-0295			352.3
P-0300			334.5
P-0301			349.9
P-0302			384.0
P-0303			400.5
P-0304			367.9
P-0305			383.9
P-0306			352.4
P-0307			352.0
P-0308			384.0
P-0309			402.5

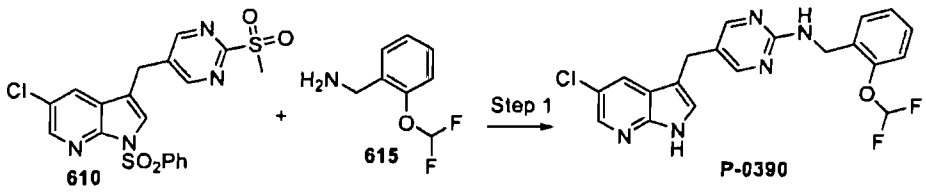
P-0310			389.0
P-0311			368.0
P-0312			382.5
P-0313			385.0
P-0314			367.9
P-0315			402.4
P-0316			368.2
P-0317			364.8
P-0318			348.6
P-0319			402.5
P-0320			402.5

P-0407			368.3

Example 38: Synthesis of [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-difluoromethoxy-benzyl)-amine P-0390

[0280] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-difluoromethoxy-benzyl)-amine **P-0390** was synthesized in 1 step from 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine 610 as shown in Scheme 194.

Scheme 194



Step 1 – Synthesis of [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-difluoromethoxy-benzyl)-amine (P-0390)

[0281] To 1-benzenesulfonyl-5-chloro-3-(2-methanesulfonyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**610**, 0.060 g, 0.13 mmol, prepared as described in Example 35, Scheme 191) in N-methylpyrrolidinone (1.40 mL) was added 2-difluoromethoxy-benzylamine (**615**, 0.200 g, 1.16 mmol). The reaction was irradiated with microwave on 300 watts, 150 °C for 15 minutes. Potassium hydroxide in water (1.00 M, 2.00 mL) was added to the reaction. The reaction was irradiated with microwave on 300 watts, 90 °C for 10 minutes, then poured into ethyl acetate and water. The organic layer was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**P-0390**, 10.9 mg, 20%). MS (ESI) $[M+H^+]^+ = 418.0$.

[0282] Additional compounds were prepared following the protocol of Scheme 194, substituting 2-difluoromethoxy-benzylamine **615** with a suitable amine. The following compounds were prepared following this protocol:

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-5-trifluoromethyl-benzyl)-amine (**P-0289**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(5-fluoro-2-trifluoromethyl-benzyl)-amine (**P-0391**),

(3-Chloro-2-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0392**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-3-trifluoromethyl-benzyl)-amine (**P-0393**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-fluoro-4-trifluoromethyl-benzyl)-amine (**P-0394**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2,3-difluoro-benzyl)-amine (**P-0395**),

(2-Chloro-4-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0396**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-trifluoromethoxy-benzyl)-amine (**P-0402**),

(2-Chloro-5-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0408**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-4-ylmethyl-amine (**P-0416**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-pyrrolidin-1-yl-ethyl)-amine (**P-0417**),

Benzyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0418**),

Benzyl-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0419**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-trifluoromethoxy-benzyl)-amine (**P-0420**),

(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0421**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-3-ylmethyl-amine (**P-0422**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-fluoro-benzyl)-amine (**P-0423**),

(3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0424**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3,5-difluoro-benzyl)-amine (**P-0425**),

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[1-(2-fluoro-phenyl)-ethyl]-amine (**P-0426**),

[1-(4-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-

amine (**P-0427**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[(S)-1-(4-fluoro-phenyl)-ethyl]-amine (**P-0428**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0429**),
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-methyl-amine (**P-0430**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methyl-benzyl)-amine (**P-0431**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-benzyl)-amine (**P-0433**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-morpholin-4-yl-ethyl)-amine (**P-0434**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-cyclohexylmethyl-amine (**P-0435**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-pyridin-2-ylmethyl-amine (**P-0436**),
[2-(4-Chloro-phenyl)-ethyl]-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0437**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-difluoromethoxy-benzyl)-amine (**P-0438**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methoxy-benzyl)-amine (**P-0439**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-methyl-benzyl)-amine (**P-0440**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-methoxy-ethyl)-amine (**P-0441**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-fluoro-benzyl)-amine (**P-0442**),
(3-Chloro-4-fluoro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-amine (**P-0443**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-ethoxy-benzyl)-amine (**P-0444**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(4-morpholin-4-yl-benzyl)-amine (**P-0445**),
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(3-difluoromethoxy-benzyl)-

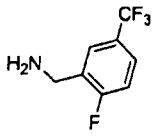
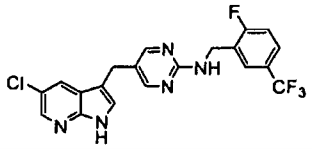
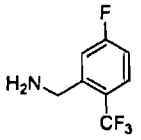
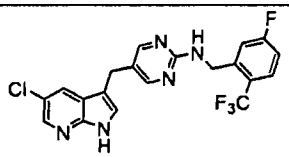
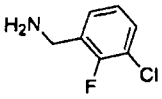
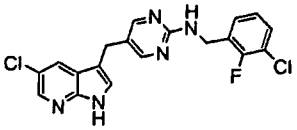
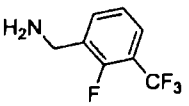
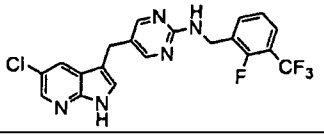
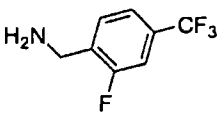
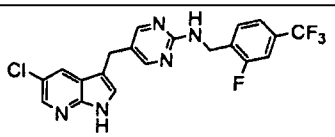
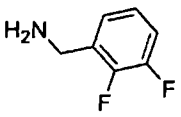
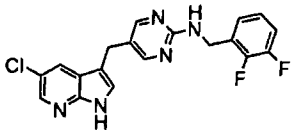
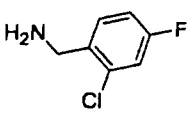
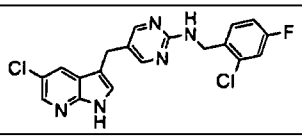
amine (**P-0446**),

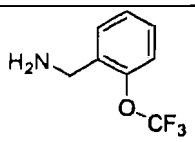
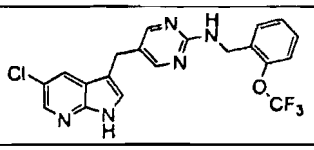
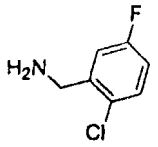
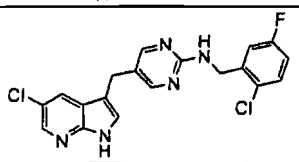
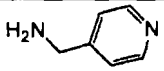
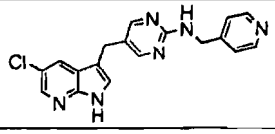
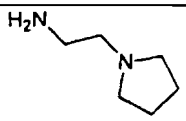
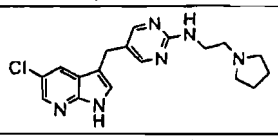
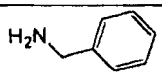
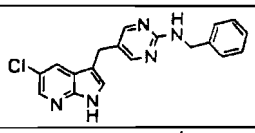
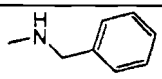
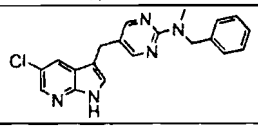
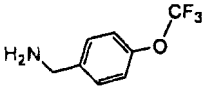
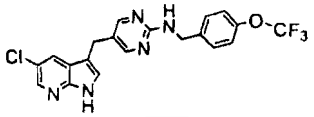
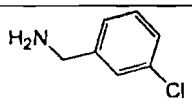
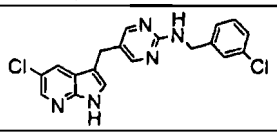
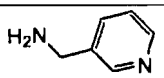
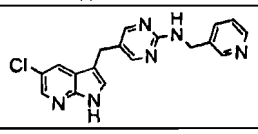
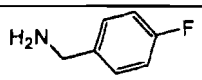
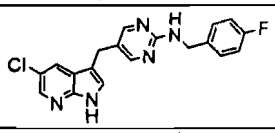
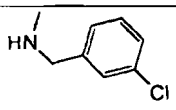
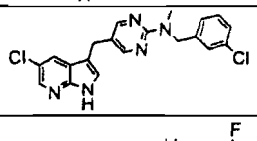
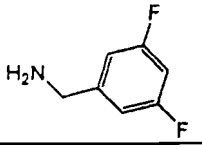
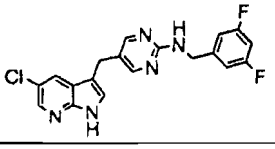
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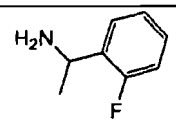
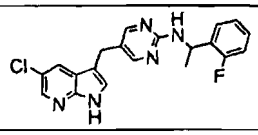
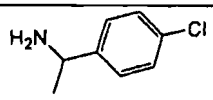
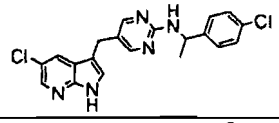
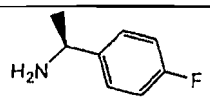
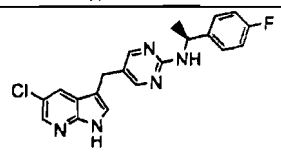
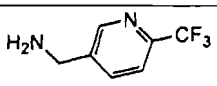
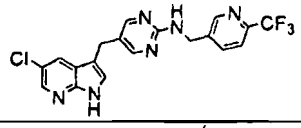
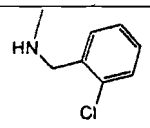
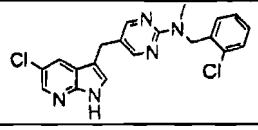
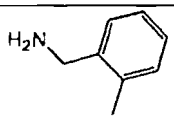
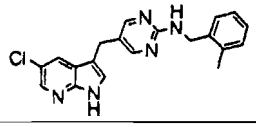
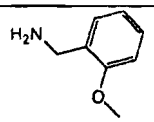
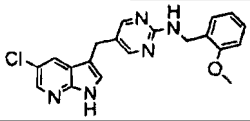
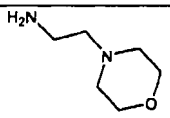
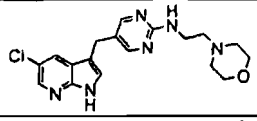
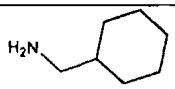
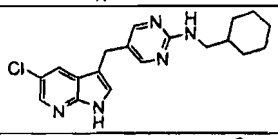
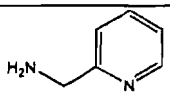
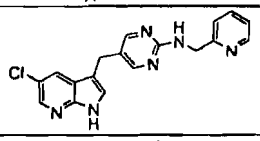
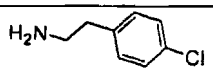
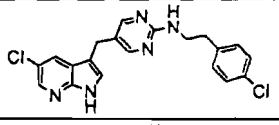
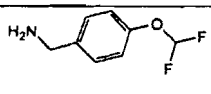
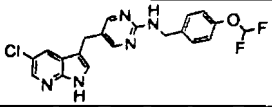
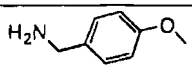
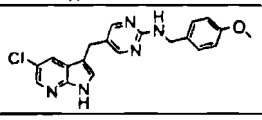
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-[1-(3-fluoro-phenyl)-ethyl]-amine (**P-0448**), and

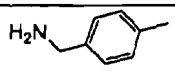
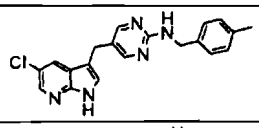
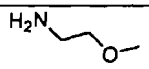
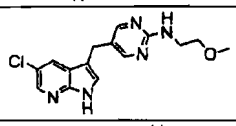
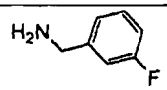
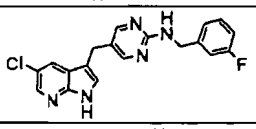
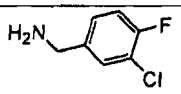
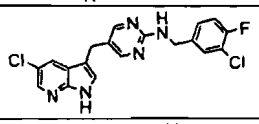
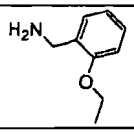
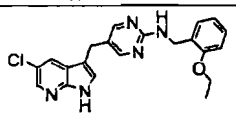
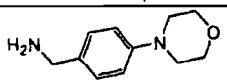
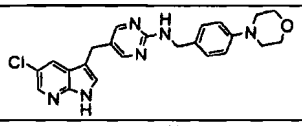
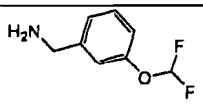
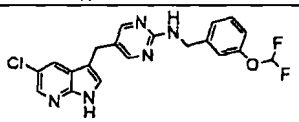
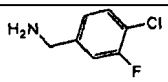
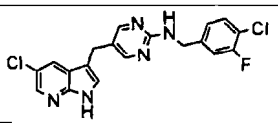
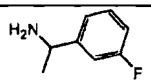
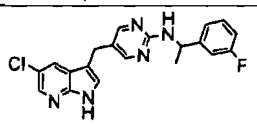
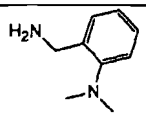
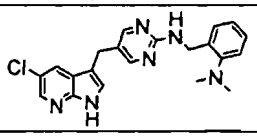
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrimidin-2-yl]-(2-dimethylamino-benzyl)-amine (**P-0449**).

The following table indicates the amine (Column 2) used in Scheme 194 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

Compound number	Amine	Compound	MS (ESI) $[M+H^+]^+$ observed
P-0289			436.0
P-0391			436.0
P-0392			402.0
P-0393			$[M-H^+]^-$ = 434.1
P-0394			437.3
P-0395			386.0
P-0396			402.0

P-0402			434.3
P-0408			402.0
P-0416			351.1
P-0417			357.1
P-0418			350.3
P-0419			364.3
P-0420			434.3
P-0421			383.9
P-0422			351.1
P-0423			368.3
P-0424			398.3
P-0425			386.3

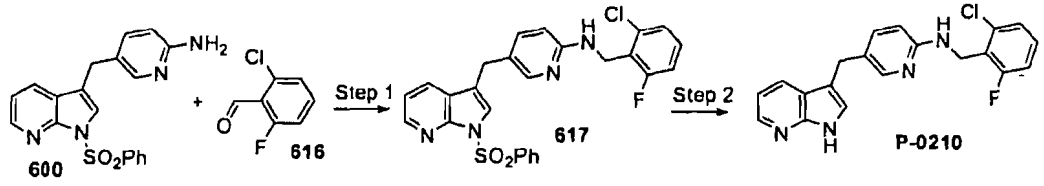
P-0426			382.3
P-0427			398.3
P-0428			382.3
P-0429			419.1
P-0430			397.9
P-0431			364.3
P-0433			380.3
P-0434			373.1
P-0435			356.3
P-0436			351.1
P-0437			397.9
P-0438			416.3
P-0439			380.3

P-0440			364.3
P-0441			317.9
P-0442			368.3
P-0443			401.9
P-0444			393.9
P-0445			435.1
P-0446			416.3
P-0447			402.3
P-0448			382.3
P-0449			393.1

Example 39: Synthesis of (2-chloro-6-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0210

[0283] (2-Chloro-6-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0210** was synthesized in 2 steps from 5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine **600** as shown in Scheme 195.

Scheme 195



Step 1 – Preparation of [5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-chloro-6-fluoro-benzyl)-amine (617):

[0284] 5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamine (**600**, 30 mg, 0.083 mmol, prepared as described in Example 29, Scheme 185) was combined with 2-chloro-6-fluoro-benzaldehyde (**616**, 26.2 mg, 0.165 mmol) in a 2 mL microwave reaction vial. The mixture was dissolved in ethanol:acetic acid (95:5, 0.6 mL). Silica supported cyanoborohydride (1.0 mmol/g, 83 mg, 0.083 mmol) was added and the mixture was irradiated with microwave on 300 watts for 5 minutes at 100 °C. The silica was separated by centrifuging and the supernatant solution was decanted. The silica residue was rinsed with ethanol (0.500 mL) and centrifuged. The solvents were combined and removed under reduced pressure to give compound **617**, which was used in the next step without further purification.

Step 2 – Preparation of (2-chloro-6-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0210):

[0285] [5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-chloro-6-fluoro-benzyl)-amine **617** was combined with methanol:potassium hydroxide (1M) (1:1, 0.5 mL). The mixture was heated at 80 °C for 2 hours. Acetic acid (0.1 mL) was added and the solvents removed under reduced pressure. The remaining residue was dissolved in dimethylsulfoxide (0.4 mL) and purified by reverse phase HPLC on a Phenomenex column (50mm x 10mm ID) eluting with 0.1 % trifluoroacetic acid in water and 20-100 % acetonitrile with 0.1% trifluoroacetic acid over 16 minutes at a flow rate of 6 mL/minute to provide the desired compound **P-0210**. MS (ESI) $[M+H^+]^+ = 367.1$.

[0286] Additional compounds were prepared following the protocol of Scheme 195, replacing 2-chloro-6-fluoro-benzaldehyde **616** with an appropriate aldehyde in Step 1. The following compounds were made following this procedure:

Phenethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0211**),

(2,4-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0212**),

(2-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0213**),

(3-Bromo-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0214**),

(2-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0215**),

(2-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0216**),

(2-Methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0217**),

(1-Methyl-1H-benzoimidazol-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0218**),

(6-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0219**),

(1H-Benzoimidazol-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0220**),

(2-Chloro-4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0221**),

(5-Methoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0222**),

(3-Fluoro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0223**),

(6-Methoxy-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0224**),

(4-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0225**),

[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0226**),

(3,5-Dichloro-pyridin-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0227**),

(6-Morpholin-4-yl-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0228**),

(3-Fluoro-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0229**),

(5-Fluoro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0230**),

(2,4-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0342**),

(3-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0343**),

(2-Fluoro-4-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0344**),

(4-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0345**),

(3-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0346**),

(2-Morpholin-4-yl-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0347**),

(4-Chloro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0348**),

(2-Chloro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0349**),

(2-Fluoro-5-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0350**),

(2,3-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0351**),

(2-Fluoro-3-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0352**),

Dimethyl-(5-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-amine (**P-0353**),

(3-Chloro-2-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0354**),

(5-Fluoro-pyridin-2-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0355**),

(3,5-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0356**),

(2-Propoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0357**),

(2-Morpholin-4-yl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0358**),

(2-Chloro-3-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0359**),

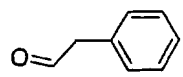
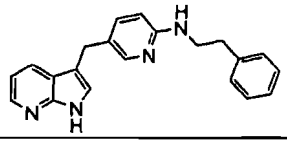
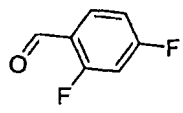
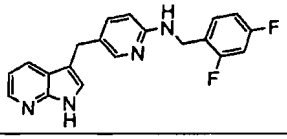
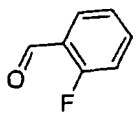
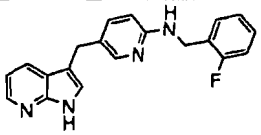
(2-Fluoro-6-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0360**),

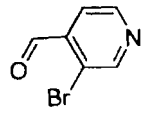
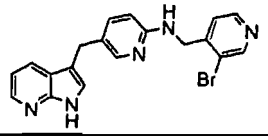
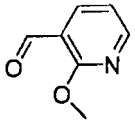
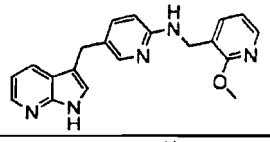
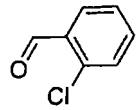
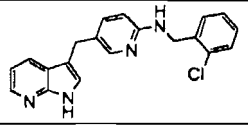
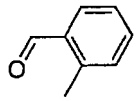
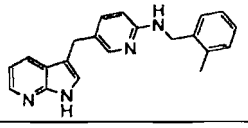
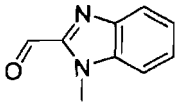
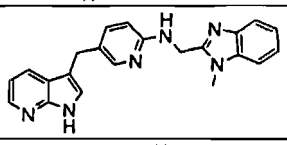
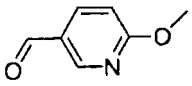
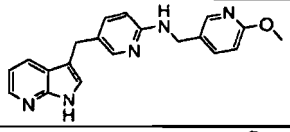
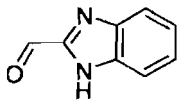
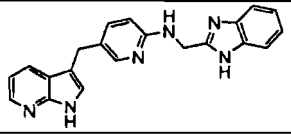
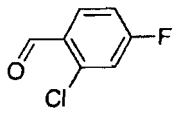
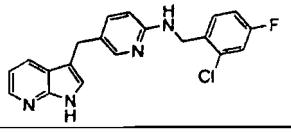
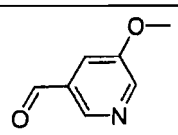
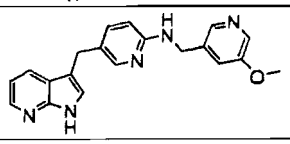
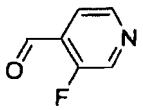
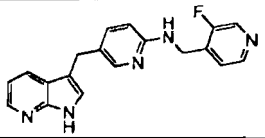
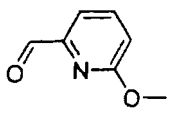
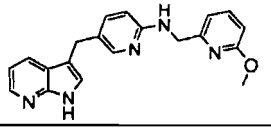
[2-(2-Morpholin-4-yl-ethoxy)-benzyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-

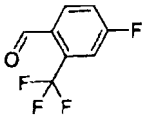
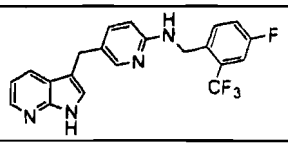
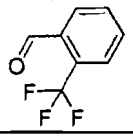
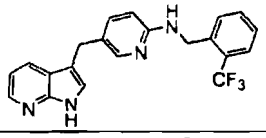
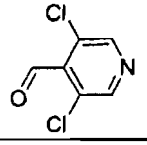
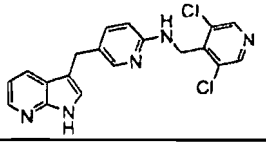
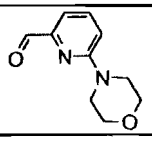
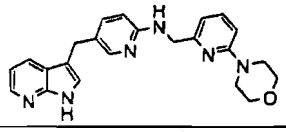
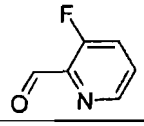
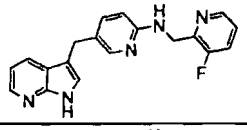
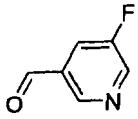
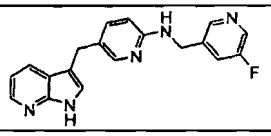
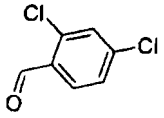
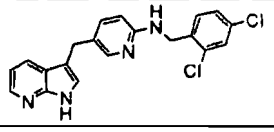
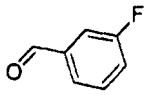
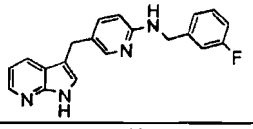
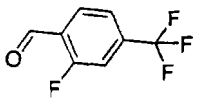
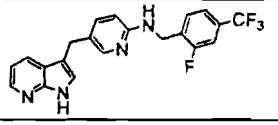
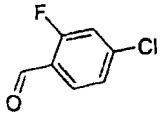
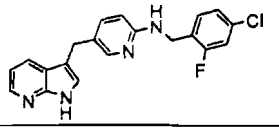
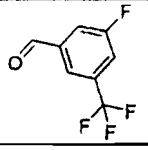
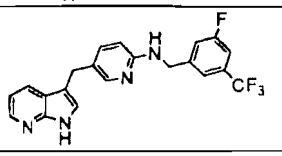
amine (**P-0361**),
(2,3-Difluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0362**),
(2-Chloro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0363**),
(2-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0364**),
(2-Fluoro-3-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0365**),
(5-Fluoro-2-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0366**),
(2-Difluoromethoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0367**),
(2-Fluoro-4-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0368**),
[2-(3-Dimethylamino-propoxy)-benzyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0369**),
(2,6-Dimethoxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0370**),
(2-Fluoro-5-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0371**),
(4-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0372**),
(3-Chloro-5-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0373**),
(6-Cyclopentyloxy-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0374**),
(5-Fluoro-2-trifluoromethyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0375**),
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[2-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine (**P-0376**),
Propane-1-sulfonic acid (2-fluoro-3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-phenyl)-amide (**P-0377**),
(2,5-Dichloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0380**),
Pyrimidin-5-ylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0381**),
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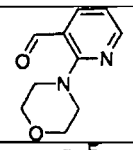
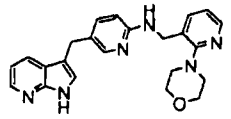
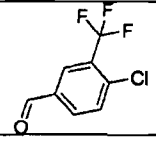
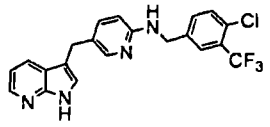
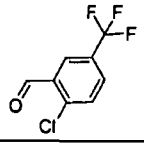
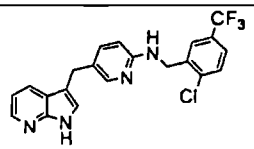
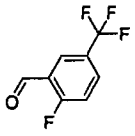
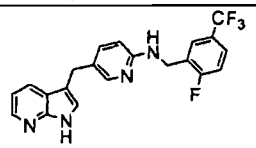
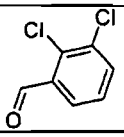
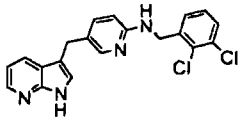
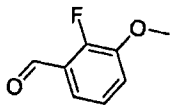
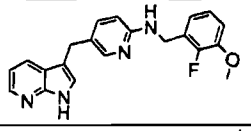
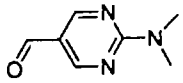
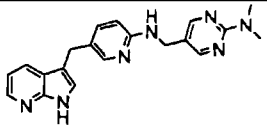
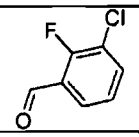
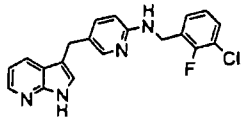
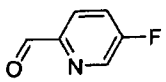
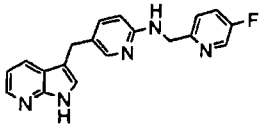
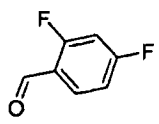
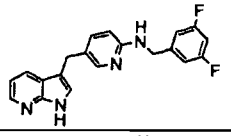
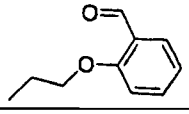
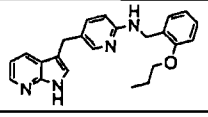
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2,2-Dimethyl-N-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-propionamide (**P-0384**),
Methyl-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-amine (**P-0385**),
Methyl-(5-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyrimidin-2-yl)-amine (**P-0386**),
(2-Chloro-4-methanesulfonyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0387**),
(5-Fluoro-2-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0397**),
(2,2-Difluoro-benzo[1,3]dioxol-4-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0398**),
Dimethyl-(3-{[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-pyridin-2-yl)-amine (**P-0399**),
(5-Chloro-pyridin-3-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0400**), and
(2-Methoxy-pyrimidin-5-ylmethyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0401**).

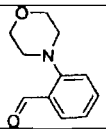
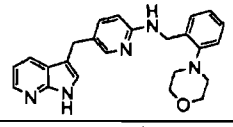
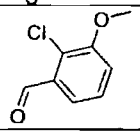
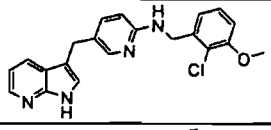
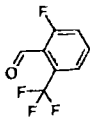
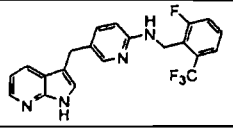
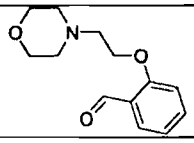
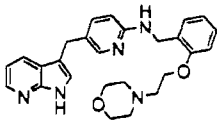
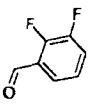
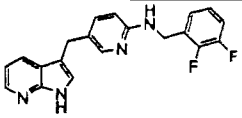
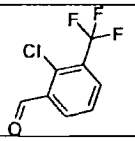
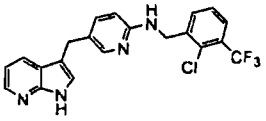
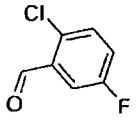
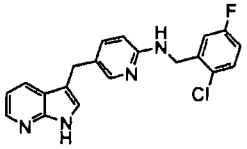
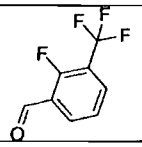
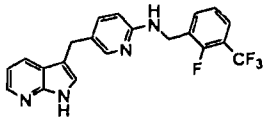
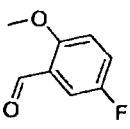
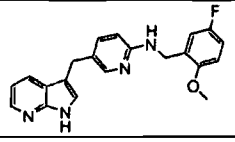
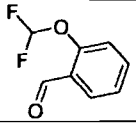
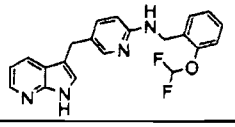
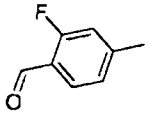
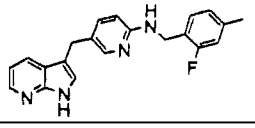
The following table indicates the aldehyde (Column 2) used in Step 1 of Scheme 195 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

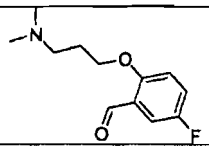
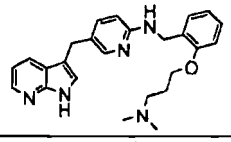
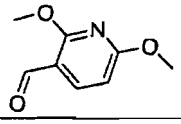
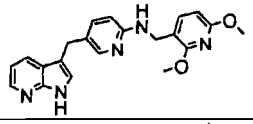
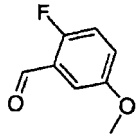
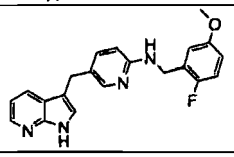
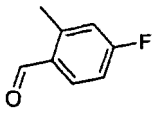
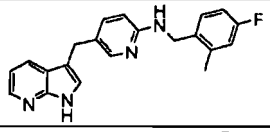
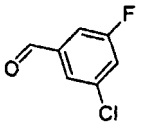
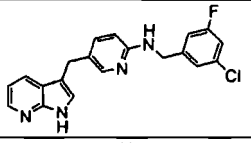
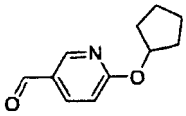
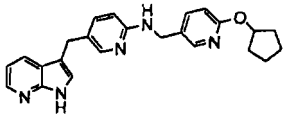
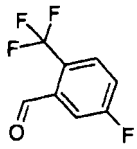
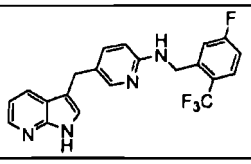
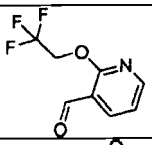
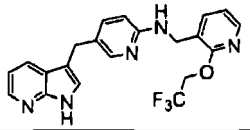
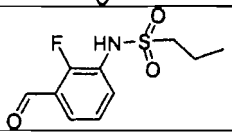
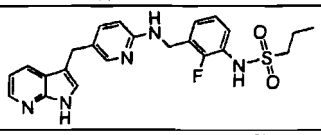
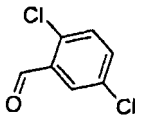
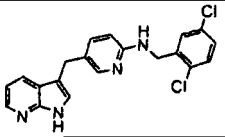
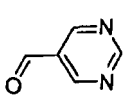
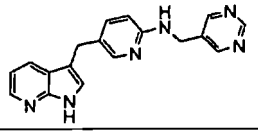
Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0211			329.1
P-0212			351.1
P-0213			338.1

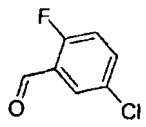
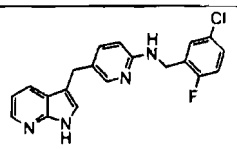
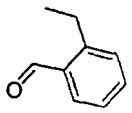
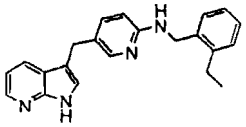
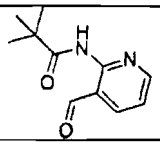
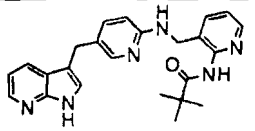
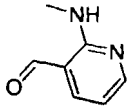
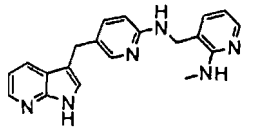
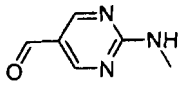
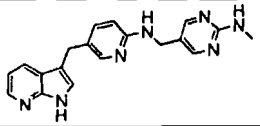
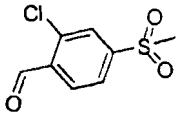
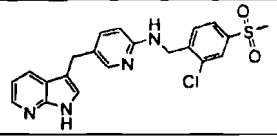
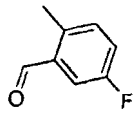
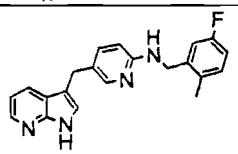
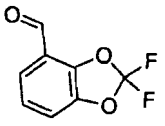
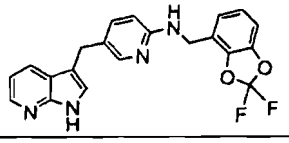
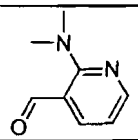
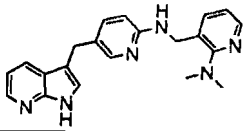
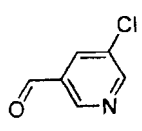
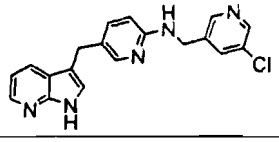
Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0214			395.9
P-0215			345.9
P-0216			349.1
P-0217			329.1
P-0218			369.1
P-0219			345.9
P-0220			355.1
P-0221			367.1
P-0222			345.9
P-0223			334.3
P-0224			345.9

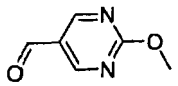
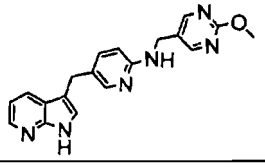
Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0225			401.1
P-0226			383.1
P-0227			383.9
P-0228			401.1
P-0229			334.3
P-0230			334.3
P-0342			383.1
P-0343			333.1
P-0344			401.1
P-0345			367.1
P-0346			401.1

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0347			401.1
P-0348			417.1
P-0349			417.1
P-0350			401.1
P-0351			383.1
P-0352			363.1
P-0353			360.3
P-0354			367.1
P-0355			334.3
P-0356			351.1
P-0357			373.1

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0358			400.3
P-0359			379.1
P-0360			401.1
P-0361			444.3
P-0362			351.1
P-0363			417.1
P-0364			367.1
P-0365			401.1
P-0366			363.1
P-0367			381.1
P-0368			347.1

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0369			416.3
P-0370			376.3
P-0371			363.1
P-0372			347.1
P-0373			367.1
P-0374			400.3
P-0375			401.1
P-0376			413.9
P-0377			453.9
P0380			383.1
P-0381			317.2

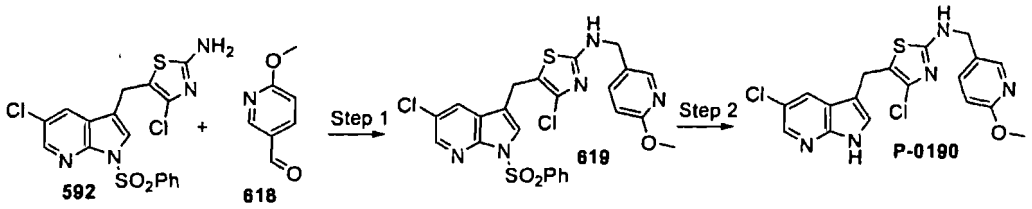
Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0382			367.1
P-0383			343.1
P-0384			415.2
P-0385			345.4
P-0386			345.2
P-0387			427.1
P-0397			347.1
P-0398			396.1
P-0399			359.1
P-0400			350.3

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0401			347.1

Example 40: Synthesis of [4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine P-0190

[0287] [4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine P-0190 was synthesized in 2 steps from 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **592** as shown in Scheme 196.

Scheme 196



*Step I – Preparation of [5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**619**):*

[0288] 5-(1-Benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine (**592**, 30 mg, 0.083 mmol, prepared as described in Example 27, Scheme 183) was combined with 6-methoxy-pyridine-3-carbaldehyde (**618**, 26.2 mg, 0.165 mmol) in a 2 mL microwave reaction vial. The mixture was dissolved in ethanol: acetic acid (95:5, 0.6 mL). Silica supported cyanoborohydride (1.0 mmol/g, 83 mg, 0.083 mmol) was added and the mixture was irradiated with microwave on 300 watts for 5 minutes at 100 °C. The silica was separated by centrifuging and the supernatant solution was decanted. The silica residue was rinsed with ethanol (0.500 mL) and centrifuged. The solvents were combined and removed under reduced pressure to give the desired compound **619**, which was used without further purification.

*Step II – Preparation of [4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine (**P-0190**):*

[0289] [5-(1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine **619** was combined with methanol: potassium hydroxide (1M) (1:1, 0.5 mL). The mixture was heated at 80 °C for 2 hours. Acetic acid (0.1 mL) was added and the solvents removed under reduced pressure. The remaining residue was dissolved in dimethylsulfoxide (0.4 mL) and purified by reverse phase HPLC on a Phenomenex column (50mm x 10mm ID) eluting with 0.1 % trifluoroacetic acid in water and 20-100 % acetonitrile with 0.1% trifluoroacetic acid over 16 minutes at a flow rate of 6 mL/minute to provide the desired compound **P-0190**. MS (ESI) $[M+H^+]^+ = 419.9$.

[0290] Additional compounds were prepared following the protocol of Scheme 196, replacing 6-methoxy-pyridine-3-carbaldehyde **618** with a suitable aldehyde in Step 1. The following compounds were made following this procedure:
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-thiazol-2-ylmethyl-amine (**P-0189**),
Benzyl-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-0192**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-methoxy-benzyl)-amine (**P-0193**),
(4-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-0194**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine (**P-0195**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-dimethyl-thiazol-5-ylmethyl)-amine (**P-0196**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-5-methyl-3H-imidazol-4-ylmethyl)-amine (**P-0197**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-2H-pyrazol-3-ylmethyl)-amine (**P-0198**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methoxy-pyridin-2-ylmethyl)-amine (**P-0199**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-fluoro-pyridin-4-ylmethyl)-amine (**P-0200**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methyl-thiazol-4-ylmethyl)-amine (**P-0201**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-methyl-thiazol-5-ylmethyl)-amine (**P-0202**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-chloro-pyridin-2-

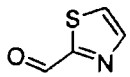
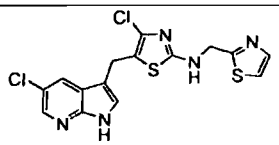
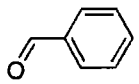
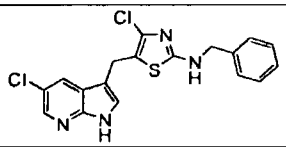
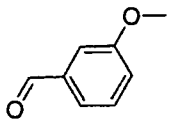
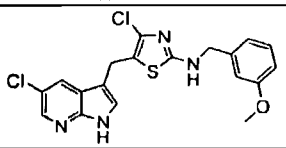
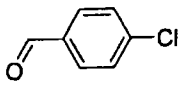
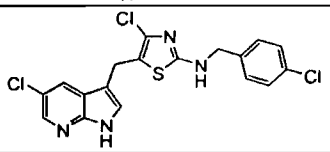
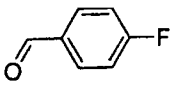
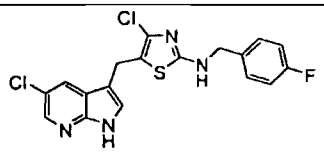
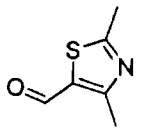
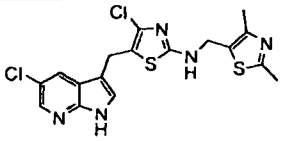
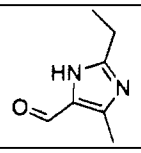
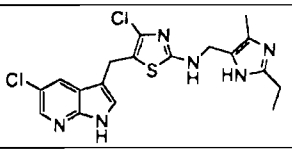
ylmethyl)-amine (**P-0203**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine (**P-0236**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-pyridin-4-ylmethyl-amine (**P-0237**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(3-chloro-pyridin-4-ylmethyl)-amine (**P-0238**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(1-ethyl-1H-pyrazol-4-ylmethyl)-amine (**P-0239**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine (**P-0240**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-methoxy-pyridin-3-ylmethyl)-amine (**P-0241**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (**P-0242**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-chloro-6-fluoro-benzyl)-amine (**P-0243**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-phenethyl-amine (**P-0244**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-difluoro-benzyl)-amine (**P-0245**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-fluoro-benzyl)-amine (**P-0246**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine (**P-0247**),
(2-Chloro-benzyl)-[4-chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (**P-0248**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-methyl-benzyl)-amine (**P-0249**),
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-chloro-4-fluoro-benzyl)-amine (**P-0250**),
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[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-morpholin-4-yl-pyridin-2-ylmethyl)-amine (**P-0252**),
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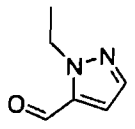
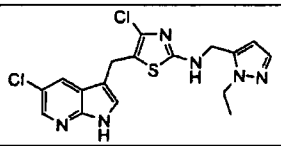
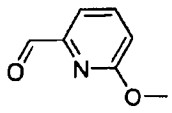
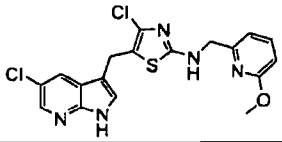
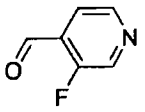
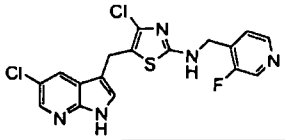
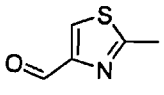
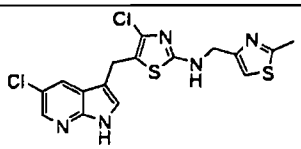
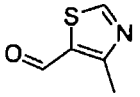
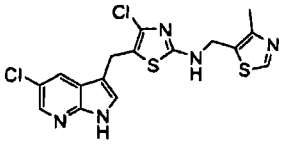
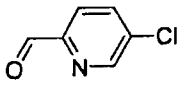
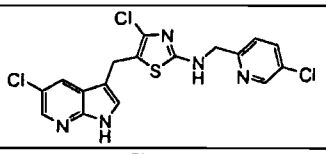
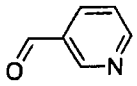
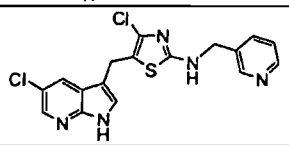
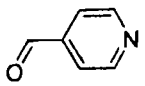
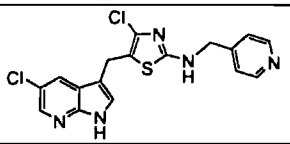
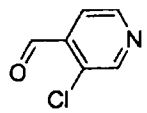
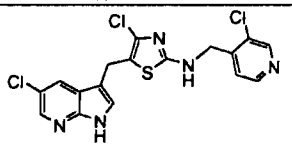
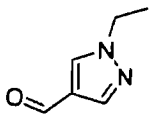
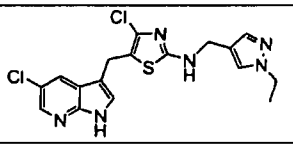
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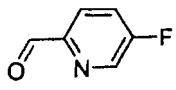
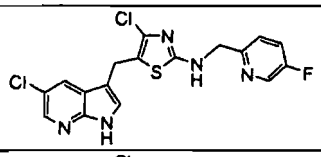
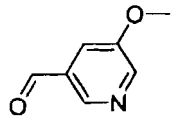
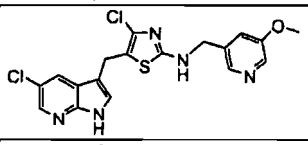
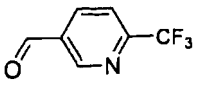
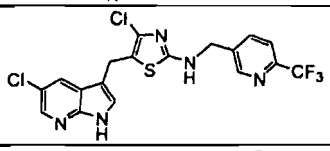
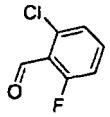
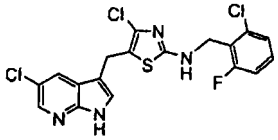
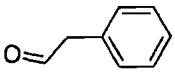
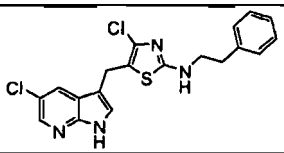
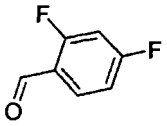
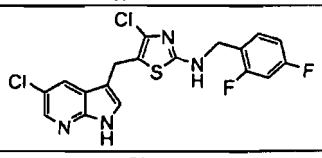
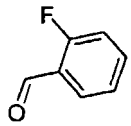
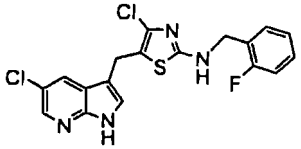
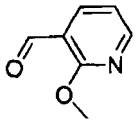
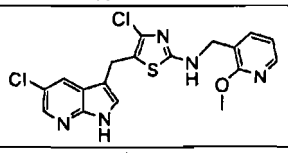
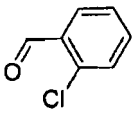
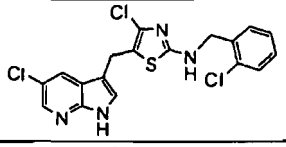
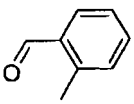
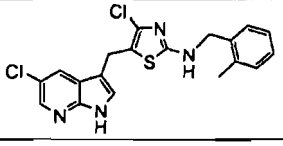
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-trifluoromethyl-benzyl)-amine (**P-0254**), and

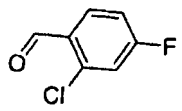
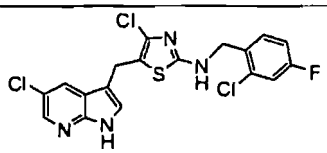
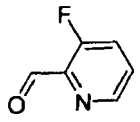
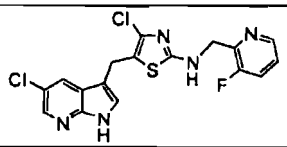
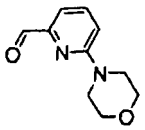
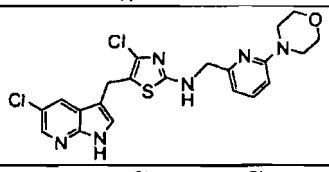
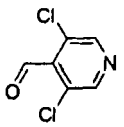
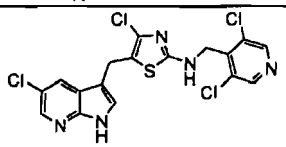
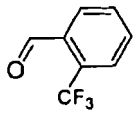
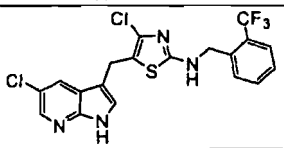
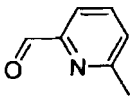
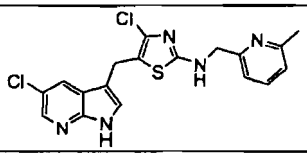
[4-Chloro-5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(6-methyl-pyridin-2-ylmethyl)-amine (**P-0255**).

The following table indicates the aldehyde (Column 2) used in Step 1 of Scheme 196 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0189			395.9
P-0192			389.1
P-0193			419.1
P-0194			425.1
P-0195			407.1
P-0196			423.9
P-0197			421.1

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0198			407.1
P-0199			419.9
P-0200			407.9
P-0201			409.9
P-0202			409.9
P-0203			423.9
P-0236			390.3
P-0237			390.3
P-0238			425.9
P-0239			407.1

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0240			407.9
P-0241			419.9
P-0242			458.3
P-0243			443.1
P-0244			403.1
P-0245			424.7
P-0246			407.1
P-0247			419.9
P-0248			424.7
P-0249			403.1

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0250			441.1
P-0251			407.9
P-0252			475.1
P-0253			459.9
P-0254			457.1
P-0255			404.3

[0291] Additional compounds were prepared following the protocol of Scheme 196, replacing 5-(1-benzenesulfonyl-5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **592** with 5-(1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-4-chloro-thiazol-2-ylamine **593** (prepared as described in Example 27, Scheme 183) in addition to replacing 6-methoxy-pyridine-3-carbaldehyde **618** with a suitable aldehyde in Step 1. The following compounds were made following this procedure:

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,4-dimethyl-thiazol-5-ylmethyl)-amine (**P-0204**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2-ethyl-5-methyl-3H-imidazol-4-ylmethyl)-amine (**P-0205**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-fluoro-pyridin-2-ylmethyl)-amine (**P-0206**),

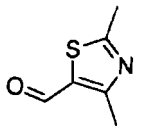
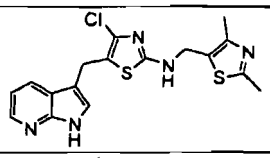
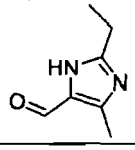
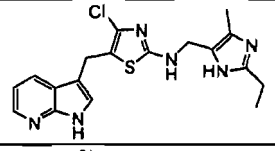
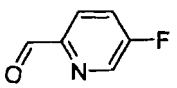
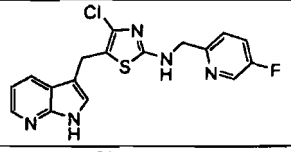
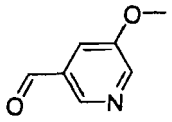
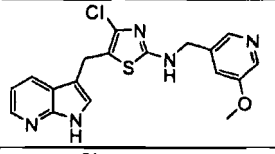
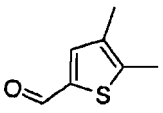
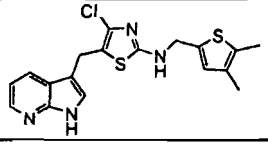
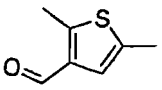
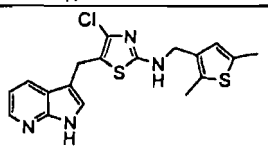
[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(5-methoxy-pyridin-3-ylmethyl)-

amine (**P-0207**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4,5-dimethyl-thiophen-2-ylmethyl)-amine (**P-0208**),

[4-Chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(2,5-dimethyl-thiophen-3-ylmethyl)-amine (**P-0209**),

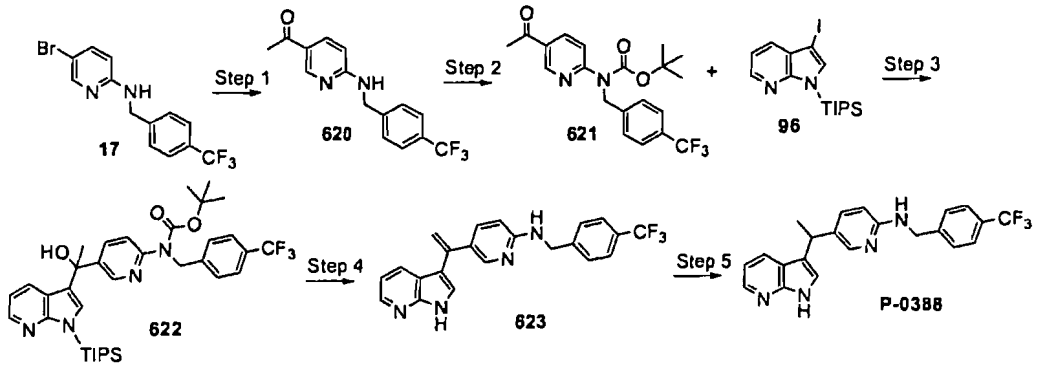
The following table indicates the aldehyde (Column 2) used in Step 1 of Scheme 196 to provide the compounds (Column 3). Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

Compound number	Aldehyde	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0204			390.3
P-0205			387.1
P-0206			373.9
P-0207			386.3
P-0208			389.1
P-0209			389.1

Example 41: Synthesis of 5-[1-(1H-pyrrolo[2,3-b]pyridin-3-yl)-ethyl]-pyridin-2-yl-(4-trifluoromethyl-benzyl)-amine P-0388

[0292] 5-[1-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-ethyl]-pyridin-2-yl-(4-trifluoromethyl-benzyl)-amine **P-0388** was synthesized from (5-bromo-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-amine **17** as shown in Scheme 197.

Scheme 197



Step 1 - Preparation of 1-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-ethanone (620):

[0293] (5-Bromo-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-amine (**17**, 3.00 g, 9.06 mmol) was dissolved in tetrahydrofuran (80 mL). The reaction was cooled at -78 °C under an atmosphere of argon. 2.5 M n-butyllithium in hexane (10.9 mL) was added. The reaction was stirred at -78 °C for 60 minutes. N-Methoxy-N-methylacetamide (1.93 mL, 18.1 mmol) was added to the reaction, which was allowed to warm to room temperature. The reaction was poured into 1M ammonium chloride and brine and extracted with ethyl acetate. The organic portions were dried with anhydrous sodium sulfate, filtered and the filtrate was adsorbed onto silica. The mixture was purified by silica gel chromatography (ethyl acetate:hexanes) to provide the desired compound as an oil that crystallized to a white solid (**620**, 1.328 g, 50%), consistent with the compound structure by ^{1}H-NMR and MS(ESI): $[M+H^+]^+$=295.3.

Step 2 - Preparation of (5-acetyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (621):

[0294] To 1-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-ethanone (**620**, 1.30 g, 4.42 mmol) in tetrahydrofuran (15.0 mL) were added di-tert-butyldicarbonate (1.10 g, 5.04 mmol), 4-dimethylaminopyridine (0.0259 g, 0.21 mmol) and N,N-diisopropylethylamine (0.888 mL, 5.10 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 3 days.

The mixture was extracted with ethyl acetate and saturated sodium bicabonate. The organic portions were dried with anhydrous sodium sulfate, filtered and the filtrate was adsorbed onto silica. The mixture was purified by silica gel chromatography (0-15% ethyl acetate:hexanes) to provide the desired compound as an oil that solidified to a white solid (**621**, 1.29g, 74%), consistent with the compound structure by ^{1}H-NMR.

Step 3 - Preparation of 1-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-1-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanol (622):

[0295] 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**96**, 485.9 mg, 1.21 mmol) was dissolved in tetrahydrofuran (8 mL) at -20 °C under an atmosphere of nitrogen. 2.0 M isopropylmagnesium chloride in tetrahydrofuran (0.655 mL) was added. The reaction was stirred at -20 °C for 1 hour. Into the reaction was added (5-acetyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (**621**, 300.0 mg, 0.76 mmol) in tetrahydrofuran (6 mL) The reaction was allowed to warm to room temperature overnight. The mixture was extracted with ethyl acetate and saturated sodium bicabonate. The organic portions were dried with anhydrous sodium sulfate, filtered and the filtrate was adsorbed onto silica. The mixture was purified by silica gel chromatography on the (ethyl acetate:hexanes), to provide the desired compound as an oil (**622**, 125 mg, 29%), consistent with the compound structure by ^{1}H-NMR.

Step 4 - Preparation of 5-[1-(1H-pyrrolo[2,3-b]pyridin-3-yl)-vinyl]-pyridin-2-yl-(4-trifluoromethyl-benzyl)-amine (623):

[0296] 1-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-yl]-1-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanol (**622**, 125.0 mg, 0.22 mmol) was dissolved in acetonitrile (11.7 mL) and trifluoroacetic acid (0.175 mL, 2.3 mmol) and triethylsilane (0.292 mL, 1.8 mmol) were added. The reaction was heated to reflux overnight. The reaction was concentrated, then washed with ethyl acetate and saturated sodium bicarbonate. The organic portions were dried with anhydrous sodium sulfate, filtered and the filtrate was adsorbed onto silica. The mixture was purified by silica gel chromatography (0-60% ethyl acetate:hexanes) to provide the desired compound (**623**, 43 mg, 50%), consistent with the compound structure by ^{1}H-NMR.

Step 5 - Preparation of 5-[1-(1H-pyrrolo[2,3-b]pyridin-3-yl)-ethyl]-pyridin-2-yl-(4-trifluoromethyl-benzyl)-amine (P-0388):

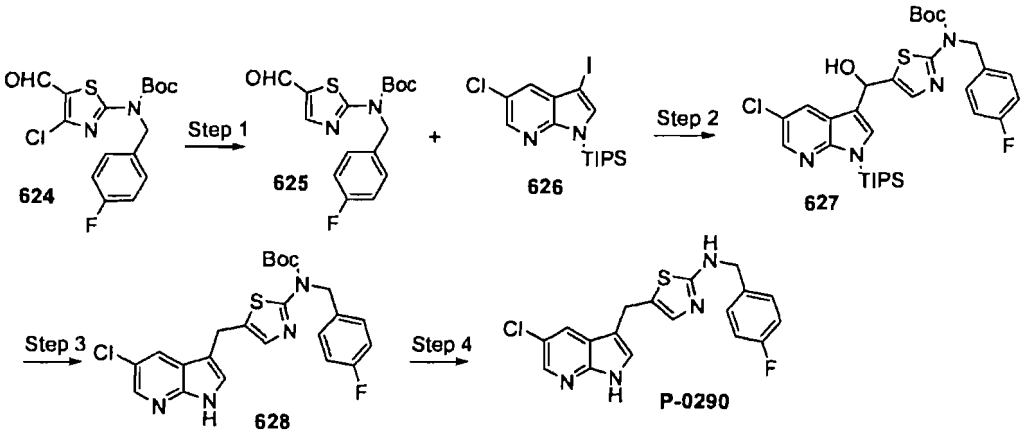
[0297] 5-[1-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-vinyl]-pyridin-2-yl-(4-trifluoromethyl-benzyl)-amine (**623**, 0.043 g, 0.00011 mol) was dissolved in tetrahydrofuran (10 mL) and methanol (10 mL). The reaction was shaken under an atmosphere of hydrogen (30 psi) overnight. The reaction was filtered through Celite and the filtrate adsorbed onto silica and purified by silica gel column chromatography (ethyl acetate:hexanes) to provide the desired compound as a white solid (**P-0388**,

2.1 mg, 5%), consistent with compound structure by ^{1}H-NMR and MS(ESI): $[M+H^+]^+$=397.6.

Example 42: Synthesis of [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine P-0290

[0298] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine **P-0290** was synthesized in four steps from (4-fluoro-benzyl)-(4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester **624** as shown in Scheme 198.

Scheme 198



Step 1 - Preparation of (4-fluoro-benzyl)-(4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (625):

[0299] To a solution of (4-fluoro-benzyl)-(4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (**624**, 1 g, 2.70 mmol, prepared as described in Example 5, Scheme 159, Step 2, where 4-(aminomethyl)pyridine **516** is replaced with p-fluorobenzylamine, i.e. intermediate in preparing compound **P-0156**) in methanol (100 mL) was added Pd/C (100 mg, 50% water wet) and sodium acetate (660 mg, 8.09 mmol) and the mixture was shaken under an atmosphere of hydrogen (50 psi) overnight observing ~50% conversion by LC/MS. The mixture was filtered over a bed of Celite and the solvent was removed *in vacuo* and purified by silica gel chromatography (ethyl acetate/heptane) to provide the desired compound as an off-white solid (450 mg, 50 %), consistent with compound structure by ^{1}H-NMR.

Step 2 - Preparation of {5-[(5-chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-thiazol-2-yl}-(4-fluoro-benzyl)-carbamic acid tert-butyl ester (627):

[0300] To a solution of 5-chloro-3-iodo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine (**626**, 300 mg, 0.69 mmol) in tetrahydrofuran (10 mL) at -20 °C was added dropwise iso-propyl-

magnesium chloride (2M in tetrahydrofuran, 0.44 mL, 0.88 mmol). The reaction mixture was allowed to warm to 0 °C over 10 minutes and then cooled to -40 °C. To this reaction mixture was added a solution of (4-fluoro-benzyl)-(4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (**625**, 211 mg, 0.63 mmol) in tetrahydrofuran (5 mL). The reaction mixture was allowed to warm to 0 °C over 30 minutes and then quenched with brine (50 mL). The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was dried over sodium sulfate and evaporated *in vacuo* to give the crude material which was purified by silica gel column chromatography (0-30% ethyl acetate/heptane) to provide the desired compound as a foam (120 mg, 30%), consistent with structure by ^{1}H-NMR.

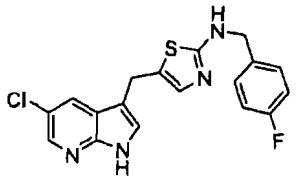
*Step 3 - Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-carbamic acid tert-butyl ester (**628**):*

[0301] To a solution of {5-[(5-chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-thiazol-2-yl}-(4-fluoro-benzyl)-carbamic acid tert-butyl ester (**627**, 120 mg, 0.186 mmol) in acetonitrile (3 mL) was added trifluoroacetic acid (0.14 mL, 1.86 mmol) and triethylsilane (0.30 mL, 1.86 mmol). The resulting mixture was stirred for 2 hours at 40 °C. The solvent was then removed *in vacuo* and the residue was used directly in the next step.

*Step 4: Preparation of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-amine (**P-0290**):*

[0302] To the solution of crude [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-(4-fluoro-benzyl)-carbamic acid tert-butyl ester (**628**, 0.186 mmol theory) in dichloromethane (5 mL) at room temperature was added trifluoroacetic acid (1 mL) and the reaction was allowed to stir overnight. The solvent was removed *in vacuo* and the residue taken up in ethyl acetate and then washed with saturated aqueous potassium carbonate making sure basicity was reached. The layers were separated and the aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated *in vacuo* to give the crude compound which was purified by silica gel chromatography (0-10% methanol/ethyl acetate). The solvent was removed *in vacuo* and the material was triturated with dichloromethane to give the desired compound as an off-white solid (20 mg, 29 % over 2 steps) consistent with compound structure by ^{1}H-NMR and MS(ESI): $[M+H^+]^+$=372.9.

[0303] (4-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine **P-0389**

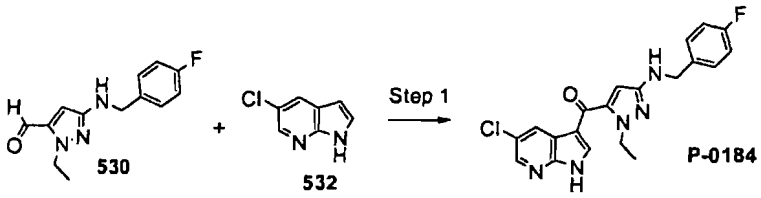


was synthesized following the protocol of Scheme 198, replacing 5-chloro-3-iodo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine **626** with 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **96**, to provide the desired compound, consistent with structure by 1H-NMR and MS(ESI): $[M+H^+]^+$=339.0.

Example 43: Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanone P-0184

[0304] (5-Chloro-1H-pyrrolo[2,3-b]pyridin- 3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanone **P-0184** was synthesized from 5-chloro-1H-pyrrolo[2,3-b]pyridine **532** in 1 step as shown in Scheme 199.

Scheme 199



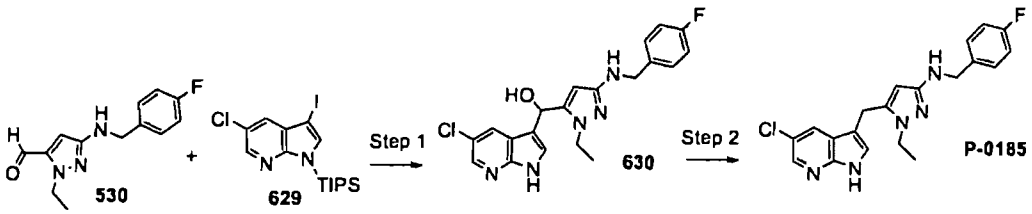
Step 1 - Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin- 3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanone (P-0184):

[0305] 5-Chloro-1H-pyrrolo[2,3-b]pyridine (**532**, 0.068 g, 0.44 mmol) was combined with methanol (10 mL) and potassium hydroxide (0.16 g, 2.8 mmol). The mixture was stirred for 50 minutes, then 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carbaldehyde (**530**, 0.100 g, 0.40 mmol, prepared as described in Example 8, Scheme 162, Step 5) was added and the reaction was stirred overnight at room temperature and then concentrated. Ethyl acetate was added and the mixture was washed with sodium bicarbonate saturated solution and brine. After drying over anhydrous sodium sulfate the solvent was removed under reduced pressure. Purification with silica gel column chromatography eluting with a gradient of ethyl acetate (10-100%) in hexanes provided the desired compound (0.0033 g, 2%). MS (ESI) $[M+H^+]^+$ = 398.1.

Example 44: Synthesis of [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-ethyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine P-0185

[0306] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-ethyl-1H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine **P-0185** was synthesized from 5-chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **629** in 2 steps as shown in Scheme 200.

Scheme 200



Step 1 - Synthesis of (5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanol (630):

[0307] 5-Chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**629**, 0.15 g, 0.34 mmol) was dissolved in tetrahydrofuran (3 mL, 40 mmol) and the solution was cooled to -20 °C. 2 M isopropylmagnesium chloride in tetrahydrofuran (200 µL) was added dropwise and the reaction was stirred and allowed to warm to -5 °C. After the reaction was cooled to -20 °C, 2-ethyl-5-(4-fluoro-benzylamino)-2H-pyrazole-3-carbaldehyde (**530**, 0.043g, 0.17 mmol, prepared as described in Example 8, Scheme162, Step 5) in tetrahydrofuran (4 mL) was added to the mixture. The reaction was stirred and allowed to warm to -5 °C, then concentrated, ethyl acetate was added and the mixture was washed with sodium bicarbonate saturated solution and brine. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure. Purification with silica gel column chromatography eluting with a gradient of ethyl acetate (5-80%) in hexanes gave the desired compound (**630**, 0.038 g, 40%).

*Step 2 - Synthesis of 5-(5-chloro-1H-pyrrolo[2,3-b]pyrid in-3-ylmethyl)-1-ethyl-1H-pyrazol-3 -yl]-(4-fluoro-benzyl)-amine (**P-0185**):*

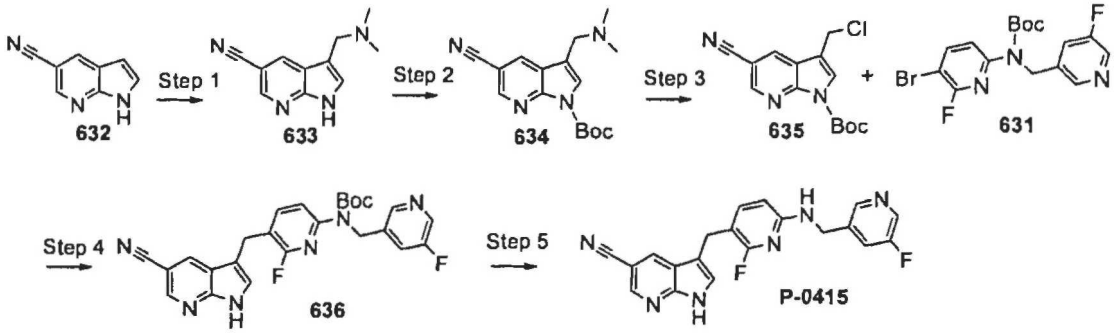
[0308] (5-Chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-ethy l-5-(4-fluoro-benzylamino)-2H-pyrazol-3-yl]-methanol (**630**, 0.045 g, 0.081 mmol) was dissolved in acetonitrile (5 mL) and triethylsilane (0.4 mL, 2.0 mmol) was added, followed by trifluoroacctic acid (0.2 mL, 2.0 mmol). The reaction was stirred at room temperature for 45 minutes, then stirred at 60 °C for 45 minutes. The solvent was removed under reduced pressure, ethyl acetate was added and the organic was washed with sodium bicarbonate saturated solution and brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to dryness. Purification with silica gel

column chromatography eluting with a gradient of ethyl acetate (40-100%) in hexanes gave the desired compound (**P-0185**, 0.0068 g, 22%). MS (ESI) $[M+H^+]^+ = 384.1$.

Example 45: Synthesis of 3-2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile P-0415

[0309] 3-2-Fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **P-0415** was synthesized in 5 steps from 1H-Pyrrolo[2,3-b]pyridine-5-carbonitrile **632** as shown in Scheme 201.

Scheme 201



Step 1 – Synthesis of 3-dimethylaminomethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (633):

[0310] To 1H-Pyrrolo[2,3-b]pyridine-5-carbonitrile (**632**, 3.00 g, 0.0210 mol) in isopropyl alcohol (120 mL) were added dimethylamine hydrochloride (1.91 g, 0.0235 mol) and formaldehyde (0.708 g, 0.0236 mol). The reaction was heated to reflux overnight, then concentrated, poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 5% to 30% methanol in dichloromethane containing 0.3% triethyl amine to give the desired compound (**633**, 2.0 g, 48%).

Step 2 – Synthesis of 5-cyano-3-dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (634):

[0311] To 3-dimethylaminomethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**633**, 2.0 g, 0.010 mol) in tetrahydrofuran (60.0 mL) were added di-tert-butyldicarbonate (2.62 g, 0.0120 mol), 4-dimethylaminopyridine (0.12 g, 0.0010 mol) and triethylamine (4.0 mL, 0.029 mol). The reaction was stirred at 45 °C over a weekend, then concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 2% to 30% methanol in dichloromethane in hexane to give the

desired compound (**634**, 2.50 g, 83%).

Step 3 – Synthesis of 3-chloromethyl-5-cyano-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (635):

[0312] To 5-cyano-3-dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**634**, 2.60 g, 8.66 mmol) in toluene (60.0 mL) under an atmosphere of nitrogen was added ethyl chloroformate (0.828 mL, 8.66 mmol). The reaction was stirred at room temperature for 3 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give a white solid (**635**, 400 mg, 16%).

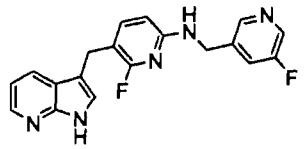
Step 4 – Synthesis of [5-(5-cyano-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (636):

[0313] To (5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**631**, 0.600 g, 1.50 mmol, prepared as described in Example 21) in tetrahydrofuran (10.0 mL) at -25 °C under an atmosphere of nitrogen, was added a solution of isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.730 mL). The reaction was allowed to warm to 5 °C over 1 hour. The reaction was cooled to -35 °C, followed by addition of a solution of CuCN.2LiCl (0.65 M in tetrahydrofuran, 2.4 mL). After 5 minutes, 3-chloromethyl-5-cyano-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**635**, 0.086 g, 0.29 mmol) in tetrahydrofuran (4.0 mL) was added to the reaction. The reaction was allowed to warm to room temperature over 1 hour, then poured into a diluted ammonia solution, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% to 100% ethyl acetate in hexane to give the desired compound (**636**, 0.13 g, 92%). MS (ESI) $[M+H^+]^+ = 477.4$.

Step 5 – Synthesis of 3-2-fluoro-6-[(5-fluoro-pyridin-3-ylmethyl)-amino]-pyridin-3-ylmethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (P-0415):

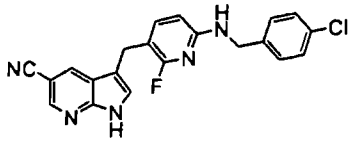
[0314] To [5-(5-cyano-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-6-fluoro-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester (**636**, 0.130 g, 0.27 mmol) in dichloromethane (10.0 mL) was added trifluoroacetic acid (1.00 mL, 0.0130 mol). The reaction was stirred at room temperature overnight. The reaction was concentrated, poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 25% to 100% ethyl acetate in hexane to give a white solid (**P-0415**, 85.6 mg, 83.4%). MS (ESI) $[M+H^+]^+ = 377.0$.

[0315] (5-Fluoro-pyridin-3-ylmethyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0414**



was prepared following the protocol of Scheme 201, substituting 1H-Pyrrolo[2,3-b]pyridine-5-carbonitrile **632** with 1H-Pyrrolo[2,3-b]pyridine in Step 1. MS (ESI) $[M+H^+]^+ = 352.5$.

[0316] 3-[6-(4-Chloro-benzylamino)-2-fluoro-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile **P-0432**

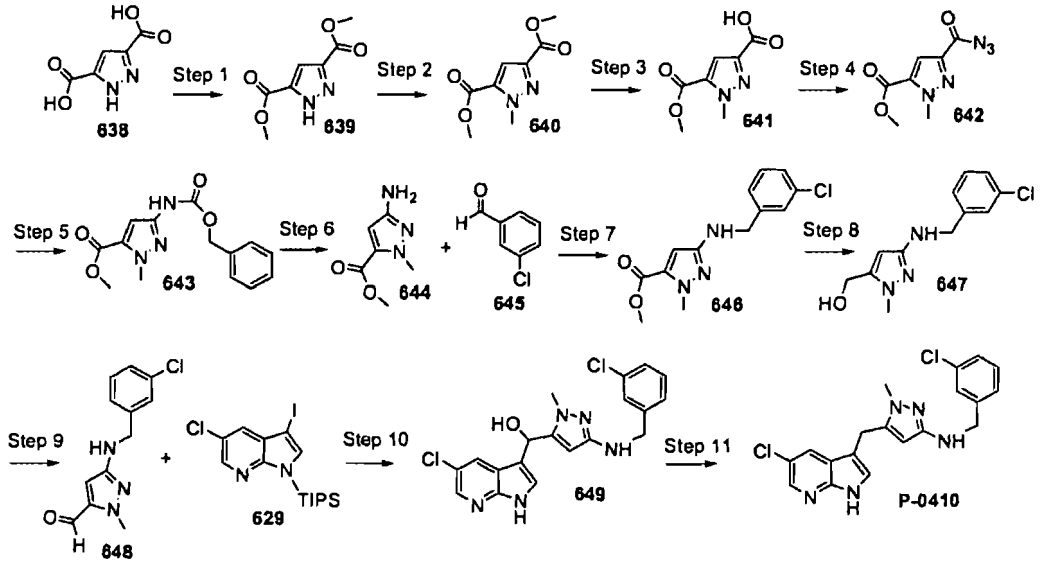


was prepared following the protocol of Scheme 201, replacing 5-bromo-6-fluoro-pyridin-2-yl)-(5-fluoro-pyridin-3-ylmethyl)-carbamic acid tert-butyl ester **631** with (5-Bromo-6-fluoro-pyridin-2-yl)-(4-chloro-benzyl)-carbamic acid tert-butyl ester **637** (prepared as described in Example 21) in Step 4. MS (ESI) $[M+H^+]^+ = 391.9$.

Example 46: Synthesis of (3-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo [2,3-b] pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-amine P-0410

[0317] (3-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo [2,3-b]pyridin-3-ylmethyl)-1- methyl-1H-pyrazol-3-yl]-amine **P-0410** was synthesized in 11 steps from 1H-pyrazole-3,5-dicarboxylic acid monohydrate **638** as shown in Scheme 202.

Scheme 202



Step 1 – Preparation of 1H-pyrazole-3,5-dicarboxylic acid dimethyl ester (639):

[0318] 1H-Pyrazole-3,5-dicarboxylic acid monohydrate (**638**, 21.1 g, 121.0 mmol) was combined with methanol (350 mL) and hydrogen chloride (10 mL). The reaction was stirred at reflux overnight and then concentrated. The resulting solid was washed with ethyl acetate and hexanes and dried under reduced pressure. The obtained compound **639** was used without further purification. MS (ESI) $[M+H^+]^+ = 185.0$.

Step 2 – Preparation of 1-methyl-1H-pyrazole-3,5-dicarboxylic acid dimethyl ester (640):

[0319] 1H-Pyrazole-3,5-dicarboxylic acid dimethyl ester (**639**, 9.1 g, 49.0 mmol) was combined with acetone (400 mL) and potassium carbonate (10.2 g, 74.1 mmol). The mixture was stirred for 40 minutes under an atmosphere of nitrogen. To the stirring suspension, methyl iodide (3.4 mL, 54.0 mmol) was added dropwise. The reaction was stirred at room temperature overnight and then the solvent was evaporated under reduced pressure. The resulting solid was washed with water and filtered. After toluene was added, the solvent was removed under reduced pressure. The resulting compound **640** was used without further purification.

Step 3 – Preparation of 1-methyl-1H-pyrazole-3,5-dicarboxylic acid 5-methyl ester (641):

[0320] 1-Methyl-1H-pyrazole-3,5-dicarboxylic acid dimethyl ester (**640**, 3.7 g, 19.0 mmol) was combined with 1,4-dioxane (20 mL) and water (60 mL). Concentrated sulfuric acid (1.0 mL) in 2 mL of water was added to the solution. After the reaction was stirred at reflux overnight, it was cooled to room temperature and concentrated until precipitation began. The obtained mixture was left standing overnight. The resulting solid was filtered and dried under reduced pressure. The

collected aqueous fractions were extracted with ethyl acetate. The organic portion was dried over anhydrous sodium sulfate and concentrated. Additional solid was crystallized from ethyl acetate to give the desired compound (**641**, 2.33 g, 68%). MS (ESI) $[M+H^+]^+ = 185.0$, melting point 175 °C.

Step 4 – Preparation of 5-azidocarbonyl-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (642):

[0321] 1-Methyl-1H-pyrazole-3,5-dicarboxylic acid 5-methyl ester (**641**, 3.2 g, 17.0 mmol) was combined with thionyl chloride (5 mL). The reaction was heated to reflux for 40 minutes and then concentrated twice from toluene. The resulting solid was dried under reduced pressure overnight. The product was dissolved into acetone (20 mL) and sodium azide (3.5 g, 54.0 mmol) was added in water (10 mL) rapidly at once. The obtained solution was stirred for one minute and then poured into ice-water (50mL). The precipitate was filtered and dried under reduced pressure. The final compound was used without further purification (**642**, 2.8 g, 77%).

Step 5 – Preparation of 5-benzyloxycarbonylamino-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (643):

[0322] 5-Azidocarbonyl-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (**642**, 2.8 g, 13.0 mmol) was combined with toluene (35 mL) and benzyl alcohol (2.1 mL, 20.0 mmol). The reaction was heated to reflux for 45 minutes and then the solvent was removed under reduced pressure. The compound (**643**, 2.4 g, 62%) was washed with methanol and dried under vacuum. MS (ESI) $[M+H^+]^+ = 290.3$.

Step 6 – Preparation of 5-amino-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (644):

[0323] 5-Benzyloxycarbonylamino-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (**643**, 2.2 g, 7.6 mmol) was combined with methanol (50 mL) and 10% palladium on carbon (500 mg). The mixture was stirred under an atmosphere of hydrogen for three hours. The mixture was filtered through Celite and the solvent was removed under reduced pressure to give the desired compound (**644**, 1.2 g, 98%). (ESI) $[M+H^+]^+ = 156.1$.

Step 7 – Preparation of 5-(3-chloro-benzylamino)-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (646):

[0324] 5-Amino-2-methyl-2H-pyrazole-3-carboxylic acid methyl ester (**644**, 1.3 g, 8.0 mmol) was combined with 3-chlorobenzaldehyde (**645**, 0.95 mL, 8.4 mmol) and acetonitrile (40 mL). Trifluoroacetic acid (3.2 mL, 42.0 mmol) was added followed by triethylsilane (6.7 mL, 42.0 mmol). The reaction was heated to reflux overnight and then concentrated. Ethyl acetate was added and the solution was washed with 1N potassium carbonate. The organic portion was dried over anhydrous sodium sulfate, filtered and concentrated. The compound (**646**, 0.944 g, 42%) was

crystallized from a mixture of ethyl acetate: hexane.

Step 8 – Preparation of [5-(3-chloro-benzylamino)-2-methyl-2H-pyrazol-3-yl]-methanol (647):

[0325] 5-(3-Chloro-benzylamino)-2-methyl-2 H-pyrazole-3-carboxylic acid methyl ester (**646**, 0.944 g, 3.37 mmol) was combined with tetrahydrofuran (20 mL) and the solution was cooled to -40 °C. 1.0 M lithium tetrahydroaluminate in tetrahydrofuran (3.7 mL) was added and the reaction was stirred for 45 min at -20 °C. 1.0 M lithium tetrahydroaluminate in tetrahydrofuran (3.7 mL) was added at -40 °C and the reaction was stirred to 10°C. Sodium sulfate decahydrate was added in small portions and the mixture was stirred for two hours at room temperature, then filtered through Celite and concentrated. The resulting compound (**647**, 0.821 g, 97%) was washed with a mixture of ethyl acetate: hexanes and dried under reduced pressure.

Step 9 – Preparation of 5-(3-chloro-benzylamino)-2-methyl-2H-pyrazole-3-carbaldehyde (648):

[0326] [5-(3-Chloro-benzylamino)-2-methyl-2H-pyrazol-3-yl]-methanol (**647**, 0.821 g, 3.26 mmol) was combined with dichloromethane (70 mL) and manganese(IV) oxide (4 g). The reaction was stirred at room temperature overnight under an atmosphere of nitrogen. The mixture was filtered through Celite and concentrated. Purification by silica gel column chromatography eluting with a gradient of ethyl acetate (10-100%) in hexane gave the desired aldehyde (**648**, 0.482 g, 60%).

Step 10 – Preparation of [5-(3-chloro-benzylamino)-2-methyl-2H-pyrazol-3-yl]-(5-chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (649):

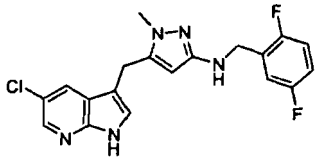
[0327] 5-Chloro-3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**629**, 0.19 g, 0.44 mmol) was dissolved in tetrahydrofuran (0.9 mL). The solution was cooled to -20 °C. 2M isopropylmagnesium chloride in tetrahydrofuran (200 μL) was added dropwise to the mixture, then stirred to -5 °C. After the reaction was cooled to -20 °C, 5-(3-chloro-benzylamino)-2-methyl-2 H-pyrazole-3-carbaldehyde (**648**, 0.050 g, 0.20 mmol) in 2 mL of tetrahydrofuran was added at once to the mixture. The reaction was stirred to 0 °C and then concentrated. Ethyl acetate was added and the mixture was washed with sodium bicarbonate saturated solution and brine. The organic portion was dried over anhydrous sodium sulfate and concentrated. Purification with silica gel column chromatography eluting with a gradient of ethyl acetate (5-80%) in hexane gave the desired compound (**649**, 0.033 g, 30%). (ESI) $[M+H^+]^+ = 558.3, 560.9$.

Step 11 – Preparation of (3-chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-amine (P-0410):

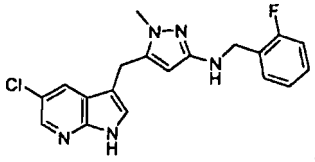
[0328] [5-(3-Chloro-benzylamino)-2-methyl-2H-pyrazol-3-yl]-(5-chloro-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**649**, 0.033 g, 0.059 mmol) was combined with

dichloromethane (5 mL, 0.08 mol) and triethylsilane (200 μL, 1.0 mmol) was added, followed by trifluoroacetic acid (100 μL, 1.0 mmol). The reaction was stirred at room temperature overnight and then concentrated. Ethyl acetate was added and the organic portion was washed with 1 M potassium carbonate, dried over anhydrous sodium sulfate and concentrated. Purification with silica gel flash chromatography eluting with a gradient of methanol (2-20%) and dichloromethane followed by washes with a mixture of ethyl acetate:hexane gave the desired compound (**P-0410**, 0.0039 g, 17%). (ESI) $[M+H^+]^+ = 387.30$.

[0329] [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(2,5-difluoro-benzyl)-amine **P-0411** and [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-1-methyl-1H-pyrazol-3-yl]-(2-fluoro-benzyl)-amine **P-0413**,



and



, respectively,

were prepared following the protocol of Scheme 202, replacing 3-chlorobenzaldehyde **645** with 2,5-difluorobenzaldehyde and 2-fluorobenzaldehyde, respectively, in Step 7. (ESI) $[M+H^+]^+ = 389.95$ (**P-0411**) and 370.20 (**P-0413**).

Example 47: Enzyme activity assays

[0330] Assays for the activity of c-Kit or c-Fms are known in the art, for example as described in US Patent Application Publication number US 2007/0032519, the disclosure of which is hereby incorporated by reference in its entirety. Similar assays may be used to assess the activity of TrkA, TrkB, and HGK.

[0331] Additional cell based assays can be correlated to the Fms activity of compounds of the invention. For example, the ability of osteoclast precursor cells (commercially available from Lonza) to differentiate into mature osteoclasts, due to stimulation by M-CSF and RANKL, in the presence of compounds, can be measured using a method analogous to that previously reported (Hudson et al., Journal of Urology, 1947, 58:89-92), where the amount of acid phosphatase in the supernatant (i.e. TRAP5b excreted by mature osteoclasts) is proportional to the number of mature osteoclasts present. In another example, the ability of M-CSF-dependent murine macrophage cells (BAC1.2F5) to proliferate in the presence of compounds can be measured by culturing cells as previously described (Morgan et al., Journal of Cellular Physiology, 1987, 130:420-427) and

determining cell viability by analysis of ATP levels in the cell culture (Crouch et al., Journal of Immunological Methods, 1993, 160:81-8).

[0332] Compounds P-0092, P-0093, P-0094, P-0095, P-0096, P-0097, P-0098, P-0099, P-0100, P-0101, P-0102, P-0103, P-0104, P-0105, P-0107, P-0108, P-0109, P-0111, P-0112, P-0113, P-0114, P-0115, P-0116, P-0118, P-0120, P-0121, P-0122, P-0123, P-0125, P-0126, P-0127, P-0128, P-0129, P-0131, P-0132, P-0138, P-0143, P-0144, P-0145, P-0148, P-0154, P-0156, P-0157, P-0159, P-0161, P-0163, P-0170, P-0171, P-0173, P-0174, P-0176, P-0177, P-0179, P-0180, P-0181, P-0182, P-0186, P-0187, P-0188, P-0190, P-0192, P-0193, P-0194, P-0195, P-0197, P-0199, P-0201, P-0203, P-0205, P-0206, P-0208, P-0211, P-0212, P-0213, P-0214, P-0215, P-0216, P-0217, P-0218, P-0219, P-0221, P-0222, P-0224, P-0225, P-0226, P-0228, P-0234, P-0237, P-0239, P-0240, P-0242, P-0243, P-0244, P-0245, P-0246, P-0252, P-0253, P-0255, P-0257, P-0258, P-0259, P-0260, P-0262, P-0263, P-0264, P-0265, P-0266, P-0267, P-0268, P-0269, P-0270, P-0271, P-0272, P-0273, P-0274, P-0275, P-0276, P-0277, P-0278, P-0279, P-0280, P-0281, P-0282, P-0283, P-0284, P-0285, P-0286, P-0287, P-0288, P-0289, P-0290, P-0291, P-0294, P-0297, P-0298, P-0301, P-0302, P-0303, P-0305, P-0306, P-0307, P-0308, P-0309, P-0311, P-0312, P-0313, P-0314, P-0316, P-0319, P-0320, P-0321, P-0322, P-0323, P-0324, P-0325, P-0326, P-0327, P-0328, P-0329, P-0330, P-0331, P-0332, P-0334, P-0336, P-0337, P-0338, P-0339, P-0340, P-0341, P-0342, P-0343, P-0344, P-0345, P-0346, P-0347, P-0348, P-0350, P-0351, P-0352, P-0354, P-0355, P-0356, P-0357, P-0358, P-0359, P-0361, P-0362, P-0363, P-0365, P-0366, P-0367, P-0368, P-0369, P-0370, P-0371, P-0372, P-0373, P-0375, P-0376, P-0377, P-0378, P-0379, P-0382, P-0383, P-0385, P-0387, P-0390, P-0392, P-0393, P-0394, P-0395, P-0396, P-0402, P-0404, P-0406, P-0407, P-0408, P-0409, and P-0412 demonstrated an IC_{50} of less than 1 μM in at least one of the c-kit assays described in US Patent Application Publication number US 2007/0032519.

[0333] Compounds P-0092, P-0093, P-0094, P-0095, P-0096, P-0097, P-0098, P-0099, P-0100, P-0101, P-0102, P-0103, P-0104, P-0105, P-0106, P-0107, P-0108, P-0109, P-0110, P-0111, P-0112, P-0113, P-0114, P-0115, P-0116, P-0117, P-0118, P-0119, P-0120, P-0121, P-0122, P-0123, P-0125, P-0126, P-0127, P-0128, P-0129, P-0130, P-0131, P-0132, P-0134, P-0135, P-0136, P-0137, P-0140, P-0141, P-0142, P-0143, P-0144, P-0145, P-0146, P-0147, P-0148, P-0149, P-0150, P-0151, P-0152, P-0153, P-0154, P-0156, P-0157, P-0158, P-0159, P-0160, P-0161, P-0163, P-0164, P-0165, P-0167, P-0168, P-0169, P-0170, P-0171, P-0172, P-0173, P-0174, P-0175, P-0176, P-0179, P-0180, P-0181, P-0182, P-0183, P-0185, P-0186, P-0187, P-0188, P-0189, P-0190, P-0191, P-0192, P-0193, P-0194, P-0195, P-0196, P-0197, P-0198, P-0199, P-0200, P-0201, P-0202, P-0203, P-0204, P-0205, P-0206, P-0207,

P-0208, P-0209, P-0210, P-0211, P-0212, P-0213, P-0214, P-0215, P-0216, P-0217, P-0218, P-0219, P-0220, P-0221, P-0222, P-0223, P-0224, P-0225, P-0226, P-0227, P-0228, P-0229, P-0230, P-0231, P-0232, P-0233, P-0234, P-0235, P-0236, P-0237, P-0238, P-0239, P-0240, P-0241, P-0242, P-0243, P-0244, P-0245, P-0246, P-0247, P-0248, P-0249, P-0250, P-0251, P-0252, P-0253, P-0254, P-0255, P-0256, P-0257, P-0258, P-0259, P-0260, P-0261, P-0262, P-0263, P-0264, P-0265, P-0266, P-0267, P-0268, P-0269, P-0270, P-0271, P-0272, P-0273, P-0274, P-0275, P-0276, P-0277, P-0278, P-0279, P-0280, P-0281, P-0282, P-0283, P-0284, P-0285, P-0286, P-0287, P-0288, P-0289, P-0290, P-0291, P-0292, P-0293, P-0294, P-0295, P-0296, P-0297, P-0298, P-0299, P-0300, P-0301, P-0302, P-0303, P-0304, P-0305, P-0306, P-0307, P-0308, P-0309, P-0310, P-0311, P-0312, P-0313, P-0314, P-0315, P-0316, P-0317, P-0318, P-0319, P-0320, P-0321, P-0322, P-0323, P-0324, P-0325, P-0326, P-0327, P-0328, P-0329, P-0330, P-0331, P-0332, P-0333, P-0334, P-0335, P-0336, P-0337, P-0338, P-0339, P-0340, P-0341, P-0342, P-0343, P-0344, P-0345, P-0346, P-0347, P-0348, P-0349, P-0350, P-0351, P-0352, P-0353, P-0354, P-0355, P-0356, P-0357, P-0358, P-0359, P-0360, P-0361, P-0362, P-0363, P-0364, P-0365, P-0366, P-0367, P-0368, P-0369, P-0370, P-0371, P-0372, P-0373, P-0374, P-0375, P-0376, P-0377, P-0378, P-0379, P-0380, P-0381, P-0382, P-0383, P-0384, P-0385, P-0386, P-0387, P-0390, P-0391, P-0392, P-0393, P-0394, P-0395, P-0396, P-0402, P-0403, P-0404, P-0405, P-0406, P-0407, P-0408, P-0409, and P-0412 had IC_{50} of less than 1 μM in at least one of the Fms assays described in US Patent Application Publication number US 2007/0032519.

[0334] Compounds were similarly assayed to determine IC_{50} values with respect to inhibition of TrkA kinase activity, for which compounds P-0157, P-0171, P-0179, P-0180, P-0303 and P-0412 had IC_{50} of less than 1 μM. in this TrkA assay. Compounds were similarly assayed to determine IC_{50} values with respect to inhibition of HGK kinase activity, for which compounds P-0156, P-0177, P-0179, P-0195, P-0201, P-0203, P-0206, P-0207, P-0231, P-0240, P-0241, P-0255, P-0324, P-0341, and P-0403 had IC_{50} of less than 1 μM.

[0335] All patents and other references cited in the specification are indicative of the level of skill of those skilled in the art to which the invention pertains, and are incorporated by reference in their entireties, including any tables and figures, to the same extent as if each reference had been incorporated by reference in its entirety individually.

[0336] One skilled in the art would readily appreciate that the present invention is well adapted to obtain the ends and advantages mentioned, as well as those inherent therein. The methods, variances, and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein

and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

[0337] It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. For example, variations can be made to provide additional compounds of Formulae II or III and/or various methods of administration can be used. Thus, such additional embodiments are within the scope of the present invention and the following claims.

[0338] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

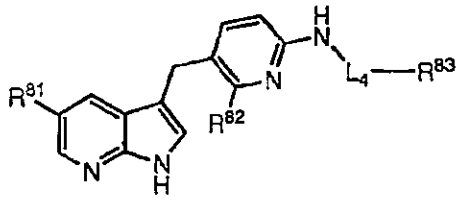
[0339] In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

[0340] Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any 2 different values as the endpoints of a range. Such ranges are also within the scope of the described invention.

[0341] Thus, additional embodiments are within the scope of the invention and within the following claims.

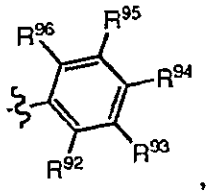
Claims

1. A compound having the chemical structure of Formula III,



or a salt, tautomer, or stereoisomer thereof,
wherein:

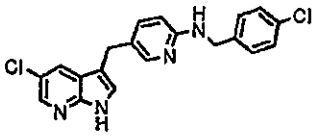
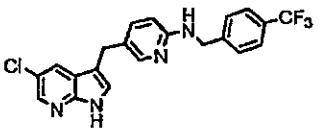
L_4 is $-CH_2-$, $-CH_2CH_2-$, $-CH(R^{40})-$, -C(O)- or -C(O)NH-;
R^{81} is chloro;
R^{82} is selected from the group consisting of hydrogen, C_{1-3} alkyl, fluoro substituted C_{2-3} alkyl, OH, C_{1-3} alkoxy, and fluoro substituted C_{1-3} alkoxy;
R^{83} is heterocycloalkyl, heteroaryl, or



in which



indicates the attachment point of R^{83} to L_4 of Formula III, wherein heterocycloalkyl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, fluoro substituted C_{1-6} alkyl, cycloalkylamino, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$;
R^{92}, R^{93}, R^{94}, R^{95}, and R^{96} are independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, fluoro substituted C_{1-6} alkyl, cycloalkylamino, $-NHS(O)_2R^{41}$, $-NHC(O)R^{41}$, $-NHR^{41}$, $-NR^{41}R^{41}$, $-OR^{41}$ and $-S(O)_2R^{41}$;
R^{40} is selected from the group consisting of C_{1-6} alkyl, and fluoro substituted C_{1-6} alkyl;
R^{41} at each occurrence is independently selected from the group consisting of C_{1-6} alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, C_{1-6} alkoxy, fluoro substituted C_{1-6} alkoxy, C_{1-6} alkylthio, fluoro substituted C_{1-6} alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{41} or as substituents of C_{1-6} alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{42}$, $-SR^{42}$, $-NHR^{42}$, $-NR^{42}R^{42}$, $-NR^{39}C(O)R^{42}$, $-NR^{39}S(O)_2R^{42}$, $-S(O)_2R^{42}$, halogen, C_{1-6} alkyl, fluoro substituted C_{1-6} alkyl, and cycloalkylamino; and
R^{42} at each occurrence is independently selected from the group consisting of C_{1-6} alkyl, heterocycloalkyl and heteroaryl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, C_{1-6} alkoxy, fluoro substituted C_{1-6} alkoxy, C_{1-6} alkylthio, fluoro substituted C_{1-6} alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein heterocycloalkyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, C_{1-6} alkyl, fluoro substituted C_{1-6} alkyl, C_{1-6} alkoxy and fluoro substituted C_{1-6} alkoxy;
provided, however, that the compound is not

2. The compound of Claim 1 selected from the group consisting of:

(3-Chloro-pyridin-4-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
Propane-1-sulfonic acid (3-{[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylamino]-methyl}-2,4-difluoro-phenyl)-amide,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine,
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-difluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,5-difluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(5-fluoro-pyridin-3-ylmethyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-difluoromethoxy-benzyl)-amine, or
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-amine; or a salt, tautomer, or stereoisomer thereof.

3. The compound of Claim 1 selected from the group consisting of:

[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine,
(3-Chloro-pyridin-4-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-difluoro-benzyl)-amine,
(2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine,
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine; or a salt, tautomer, or stereoisomer thereof.

4. The compound of Claim 1 wherein the compound is (3-Chloro-pyridin-4-ylmethyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine.

5. The compound of Claim 1 wherein the compound is [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-fluoro-benzyl)-amine.

6. The compound of Claim 1 wherein the compound is [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine.

7. The compound of Claim 1 wherein the compound is [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-trifluoromethyl-benzyl)-amine.

8. The compound of Claim 1 wherein the compound is [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2,6-difluoro-benzyl)-amine.

9. The compound of Claim 1 wherein the compound is (2-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine.

10. The compound of Claim 1 wherein the compound is [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-methoxy-pyridin-3-ylmethyl)-amine.

11. The compound of Claim 1 wherein the compound is [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(2-methoxy-pyridin-3-ylmethyl)-amine.

12. A composition comprising a pharmaceutically acceptable carrier and a compound according to any of Claims 1-11.

13. A compound of any of Claims 1-11 or a composition of claim 12 for use in a method of treating a subject suffering from or at risk of a c-kit and/or c-fms mediated disease or condition, comprising administering to the subject an effective amount of said compound or composition, wherein the disease or condition is selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, prostate cancer, canine mast cell tumors, metastasis of cancer to bone or other tissues, hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosis, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease, emphysema, atherosclerosis, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, stroke, Alzheimer's disease, Parkinson's disease, inflammatory pain, chronic pain, and bone pain.

14. The compound or composition for use of Claim 13, wherein the compound is approved for administration to a human.

15. A kit comprising a composition according to Claim 12.

16. The kit of Claim 15, wherein the composition is approved for a medical indication selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, prostate cancer, canine mast cell tumors, metastasis of cancer to bone or other tissues, hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosis, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease, emphysema, atherosclerosis, Type I diabetes, Type II diabetes, insulin resistance, hyperglycemia, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, diabetic nephropathy, stroke, Alzheimer's disease, Parkinson's disease, inflammatory pain, chronic pain, and bone pain.