

COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR

RELATED PATENT APPLICATIONS

[0001] This application claims the benefit of U.S. Prov. App. No. 60/692,960, filed June 22, 2005, and U.S. Prov. App. No. 60/731,528, filed October 28, 2005, both of which are incorporated herein by reference in their entireties and for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates to kinases and compounds which modulate kinases, and uses therefor. Particular embodiments contemplate disease indications which are amenable to treatment by modulation of kinase activity by the compounds of the present invention.

BACKGROUND OF THE INVENTION

[0003] The information provided herein 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 herein is incorporated in its entirety.

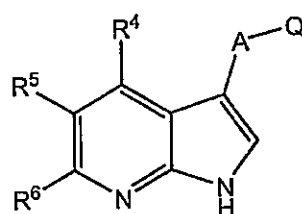
[0004] Receptor protein kinases regulate key signal transduction cascades that control or are involved in the control of a plethora of physiological functions including cellular growth and proliferation, cell differentiation, cellular development, cell division, cell adhesion, stress response, short-range contact-mediated axonal guidance, transcription regulation, aberrant mitogenesis, angiogenesis, abnormal endothelial cell-cell or cell-matrix interactions during vascular development, inflammation, lymphohematopoietic stem cell activity, protective immunity against specific bacteria, allergic asthma, aberrant tissue-specific responses to the activation of the JNK signal transduction pathway, cell transformation, memory, apoptosis, competitive activity-dependent synapse modification at the neuromuscular synapse, immunological mediation of disease, and calcium regulation. As such, a variety of specific disease states are associated with aberrant regulation of protein kinases. Accordingly, there is a need in the art for additional compounds and methods of use thereof for the modulation of receptor protein kinases in treatment of various diseases.

[0005] This application is related to the following published patent applications: WO 2004024895, US 20040142864, WO 2004078923, US 20050170431, WO 2005028624, US 20050164300, and WO 2005062795, each of which are hereby incorporated by reference herein in their entireties including all specifications, figures, and tables, and for all purposes.

SUMMARY OF THE INVENTION

[0006] The present invention concerns compounds active on protein kinases in general, including, but not limited to, B-Raf, c-Raf-1, Fms, Jnk1, Jnk2, Jnk3, and/or Kit, including any mutations of these kinases, and the use thereof in treating disease and conditions associated with regulation of the activity of the kinases. In particular, the invention concerns compounds of Formula III as described below. Thus, the invention provides novel uses of compounds for therapeutic methods involving modulation of protein kinases, as well as novel compounds that can be used for therapeutic methods involving modulation of protein kinases.

[0007] The compounds of Formula III have the following structure:

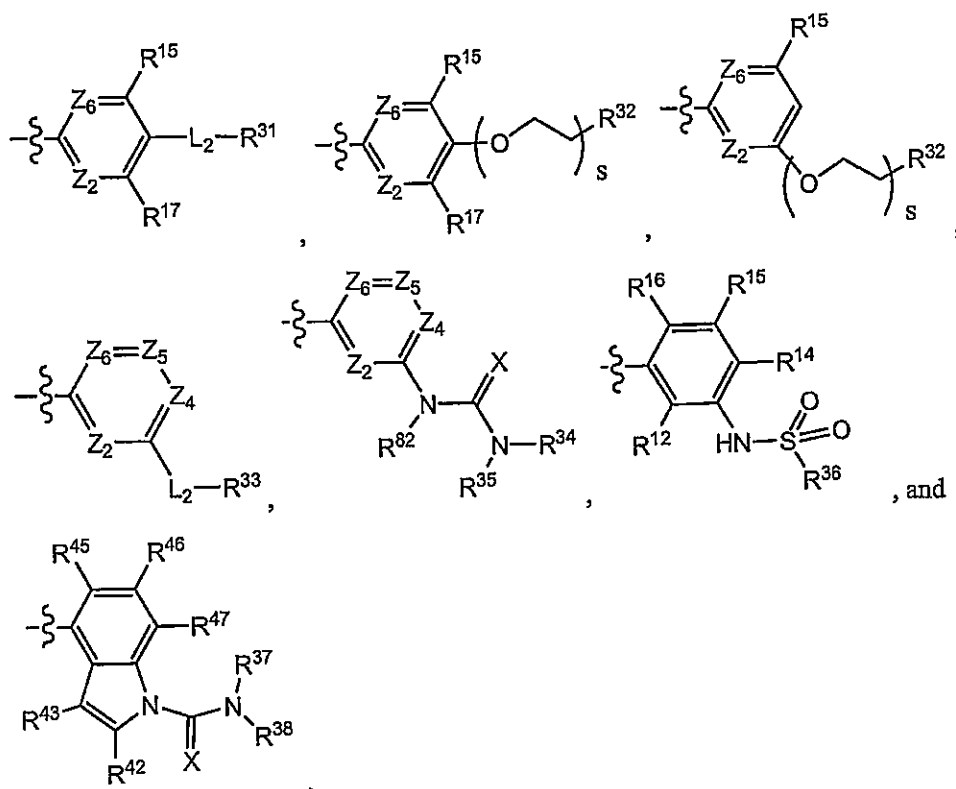


Formula III

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

Q has a structure selected from the group consisting of



in which $\text{---}\zeta\text{---}$ indicates the attachment point of Q to A of Formula III;

Z_2 is N or CR^{12} ; Z_4 is N or CR^{14} ; Z_5 is N or CR^{15} ; Z_6 is N or CR^{16} ;

L_2 is selected from the group consisting of $-(CR^{10}R^{11})_p-NR^{25}-(CR^{10}R^{11})_{q-}$,
 $-(CR^{10}R^{11})_p-O-(CR^{10}R^{11})_{q-}$, $-(CR^{10}R^{11})_p-S-(CR^{10}R^{11})_{q-}$, $-(CR^{10}R^{11})_p-C(O)-(CR^{10}R^{11})_{q-}$,
 $-(CR^{10}R^{11})_p-C(S)-(CR^{10}R^{11})_{q-}$, $-(CR^{10}R^{11})_p-S(O)-(CR^{10}R^{11})_{q-}$, $-(CR^{10}R^{11})_p-S(O)_2-(CR^{10}R^{11})_{q-}$,
 $-(CR^{10}R^{11})_p-C(O)NR^{25}-(CR^{10}R^{11})_{q-}$, $-(CR^{10}R^{11})_p-C(S)NR^{25}-(CR^{10}R^{11})_{q-}$,
 $-(CR^{10}R^{11})_p-S(O)_2NR^{25}-(CR^{10}R^{11})_{q-}$, $-(CR^{10}R^{11})_p-NR^{25}C(O)-(CR^{10}R^{11})_{q-}$,
 $-(CR^{10}R^{11})_p-NR^{25}C(S)-(CR^{10}R^{11})_{q-}$, and $-(CR^{10}R^{11})_p-NR^{25}S(O)_2-(CR^{10}R^{11})_{q-}$;

p and q are independently 0, 1, or 2 provided, however, that at least one of p and q is 0;

s is 1 or 2;

X is O or S;

A is selected from the group consisting of $-O-$, $-S-$, $-CR^aR^b$, $-NR^1$, $-C(O)-$, $-C(S)-$, $-S(O)-$, and $-S(O)_2-$;

R^a and R^b at each occurrence are independently selected from the group consisting of hydrogen, fluoro, $-OH$, $-NH_2$, lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and $-NR^8R^9$, wherein the alkyl chain(s) of lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the alkyl chain carbon bound to O of alkoxy, S of thioalkyl or N of mono- or di-alkylamino is fluoro; or

R^a and R^b combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl, wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, $-OH$, $-NH_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

R^1 is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C(O)R^7$, $-C(S)R^7$, $-S(O)_2R^7$, $-C(O)NHR^7$, $-C(S)NHR^7$, and $-S(O)_2NHR^7$, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and $-NR^8R^9$, wherein the alkyl chain(s) of lower alkoxy, lower alkylthio, mono-alkylamino, or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the alkyl chain carbon bound to O of alkoxy, S of thioalkyl or N of mono- or di-alkylamino is fluoro,

further provided that when R^1 is lower alkyl, any substitution on the lower alkyl carbon bound to the N of $-NR^1$ is fluoro, and wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, $-OH$, $-NH_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

R^7 is 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, $-OH$, $-NH_2$, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and $-NR^8R^9$, provided, however, that any substitution of the alkyl carbon bound to the N of $-C(O)NHR^7$, $-C(S)NHR^7$ or $-S(O)_2NHR^7$ is fluoro, wherein the alkyl chain(s) of lower alkoxy, lower alkylthio, mono-alkylamino, or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the alkyl chain carbon bound to O of alkoxy, S of thioalkyl or N of mono- or di-alkylamino is fluoro, and wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, $-OH$, $-NH_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

R^4 , R^5 , R^6 , R^{12} , R^{14} , R^{15} , R^{16} , R^{42} , R^{43} , R^{45} , R^{46} and R^{47} are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-CN$, $-NO_2$, $-CR^aR^bR^{26}$, and $-LR^{26}$;

L at each occurrence is independently selected from the group consisting of $-(alk)_a-S-(alk)_b-$, $-(alk)_a-O-(alk)_b-$, $-(alk)_a-NR^{25}-(alk)_b-$, $-(alk)_a-C(O)-(alk)_b-$, $-(alk)_a-C(S)-(alk)_b-$, $-(alk)_a-S(O)-(alk)_b-$, $-(alk)_a-S(O)_2-(alk)_b-$, $-(alk)_a-OC(O)-(alk)_b-$, $-(alk)_a-C(O)O-(alk)_b-$, $-(alk)_a-OC(S)-(alk)_b-$, $-(alk)_a-C(S)O-(alk)_b-$, $-(alk)_a-C(O)NR^{25}-(alk)_b-$, $-(alk)_a-C(S)NR^{25}-(alk)_b-$, $-(alk)_a-S(O)_2NR^{25}-(alk)_b-$, $-(alk)_a-NR^{25}C(O)-(alk)_b-$, $-(alk)_a-NR^{25}C(S)-(alk)_b-$, $-(alk)_a-NR^{25}S(O)_2-(alk)_b-$, $-(alk)_a-NR^{25}C(O)O-(alk)_b-$, $-(alk)_a-NR^{25}C(S)O-(alk)_b-$, $-(alk)_a-OC(O)NR^{25}-(alk)_b-$, $-(alk)_a-OC(S)NR^{25}-(alk)_b-$, $-(alk)_a-NR^{25}C(O)NR^{25}-(alk)_b-$, $-(alk)_a-NR^{25}C(S)NR^{25}-(alk)_b-$, and $-(alk)_a-NR^{25}S(O)_2NR^{25}-(alk)_b-$;

a and b are independently 0 or 1;

alk is C₁₋₃ alkylene or C₁₋₃ alkylene substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and -NR⁸R⁹, wherein lower alkyl or the alkyl chain(s) of lower alkoxy, lower alkylthio, mono-alkylamino or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution of the alkyl chain carbon bound to O of alkoxy, S of thioalkyl or N of mono- or di-alkylamino is fluoro;

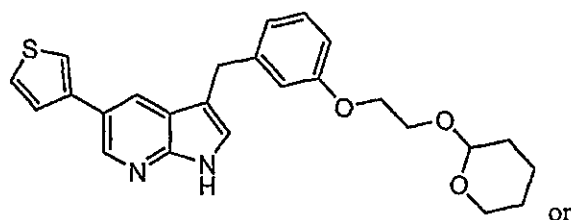
R²⁵ at each occurrence is independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R²⁶ at each occurrence is independently selected from the group consisting of hydrogen, provided, however, that hydrogen is not bound to any of S(O), S(O)₂, C(O) or C(S) of L, optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that when R²⁶ is optionally substituted lower alkenyl, no alkene carbon thereof is bound to N, S, O, S(O), S(O)₂, C(O) or C(S) of L, optionally substituted lower alkynyl, provided, however, that when R²⁶ is optionally substituted lower alkynyl, no alkyne carbon thereof is bound to N, S, O, S(O), S(O)₂, C(O) or C(S) of L, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

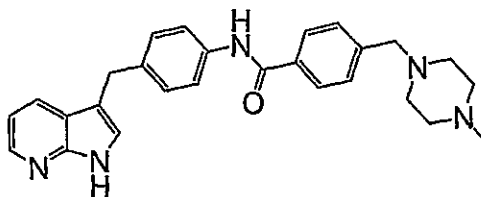
R¹⁰ and R¹¹ at each occurrence are independently selected from the group consisting of hydrogen, fluoro, lower alkyl, and lower alkyl optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or

any two of R¹⁰ and R¹¹ on the same or adjacent carbon atoms combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl, and any others of R¹⁰ and R¹¹ are independently selected from the group consisting of hydrogen, fluoro, lower alkyl, and lower alkyl optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

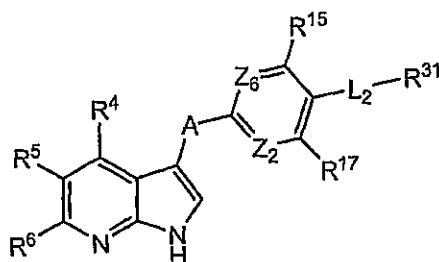
- R^8 and R^9 combine with the nitrogen to which they are attached to form a 5-7 membered heterocycloalkyl optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio;
- R^{17} is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl and -OR¹⁸;
- R^{31} and R^{33} are independently selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocycloalkyl;
- R^{36} is selected from the group consisting of substituted methyl, optionally substituted C₂₋₆ alkyl, optionally substituted lower alkenyl, provided, however, that when R^{36} is optionally substituted lower alkenyl, no alkene carbon thereof is bound to the S(O)₂ of S(O)₂R³⁶, optionally substituted lower alkynyl, provided, however, that when R^{36} is optionally substituted lower alkynyl, no alkyne carbon thereof is bound to the S(O)₂ of S(O)₂R³⁶, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and -NR¹⁹R²⁰;
- R^{19} , R^{20} , R^{34} , R^{35} , R^{37} , and R^{38} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that when R^{19} , R^{20} , R^{34} , R^{35} , R^{37} , or R^{38} is optionally substituted lower alkenyl, no alkene carbon thereof is bound to the N of NR¹⁹R²⁰, NR³⁴R³⁵ or NR³⁷R³⁸, optionally substituted lower alkynyl, provided, however, that when R^{19} , R^{20} , R^{34} , R^{35} , R^{37} , or R^{38} is optionally substituted lower alkynyl, no alkyne carbon thereof is bound to the N of NR¹⁹R²⁰, NR³⁴R³⁵ or NR³⁷R³⁸, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl; or
- R^{34} and R^{35} together with the nitrogen to which they are attached form optionally substituted 5-7 membered heterocycloalkyl or optionally substituted 5 or 7 membered nitrogen containing heteroaryl; or
- R^{37} and R^{38} together with the nitrogen to which they are attached form optionally substituted 5-7 membered heterocycloalkyl or optionally substituted 5 or 7 membered nitrogen containing heteroaryl;
- R^{32} is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and -OR¹⁸;
- R^{82} is selected from hydrogen or lower alkyl; and
- R^{18} is hydrogen or optionally substituted lower alkyl;
- provided, however, that the compound is not 3-{3-[2-(tetrahydropyran-2-yloxy)-ethoxy]-benzyl}-5-thiophen-3-yl-1H-pyrrolo[2,3-b]pyridine, which has the structure



4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-benzamide, which has the structure



[0008] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIa:



Formula IIIa

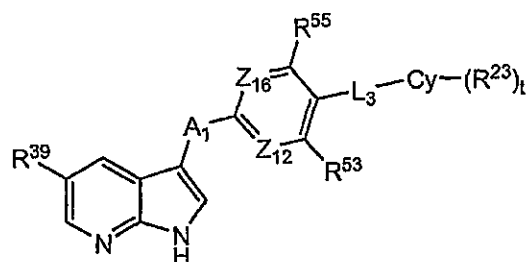
all salts, prodrugs, tautomers and isomers thereof, wherein A, L₂, Z₂, Z₆, R⁴, R⁵, R⁶, R¹⁵, R¹⁷ and R³¹ are as defined for Formula III.

[0009] In some embodiments of compounds of Formula IIIa, R⁴ and R⁶ are hydrogen, A is -O-, -CR^aR^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, more preferably -CH₂-, R¹⁷ is selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro, and R¹⁵ is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy.

[0010] In some embodiments of compounds of Formula IIIa, R⁴ and R⁶ are hydrogen, A is -O-, -CR^aR^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, R¹⁷ is selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower

alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro, R¹⁵ is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, Z₂ is N or CR¹², Z₆ is N or CR¹⁶, R¹² and R¹⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, and R⁵ is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, optionally substituted aryl, optionally substituted heteroaryl, and NR²¹R²², wherein R²¹ is hydrogen or lower alkyl, and R²² is hydrogen, lower alkyl, optionally substituted aryl or optionally substituted heteroaryl, and wherein the alkyl chain of R⁵, R²¹ or R²², when lower alkyl, or the alkyl chain of lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino.

[0011] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIb:



Formula IIIb

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A₁ is -O-, -CR⁴⁰R⁴¹-, -C(O)- or -NR⁴⁸-;

Z₁₂ is N or CR⁵²;

Z₁₆ is N or CR⁵⁶;

R⁴⁰ and R⁴¹ are independently selected from the group consisting of hydrogen, fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or R⁴⁰ and R⁴¹ combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl, wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower

alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

L_3 is selected from the group consisting of $-NR^{48}$ -, $-S$ -, $-O$ -, $-NR^{48}CH(R^{49})$ -, $-SCH(R^{49})$ -, $-OCH(R^{49})$ -, $-C(O)NR^{48}$ -, $-S(O)_2NR^{48}$ -, $-CH(R^{49})NR^{48}$ -, $-CH(R^{49})O$ -, $-CH(R^{49})S$ -, $-NR^{48}C(O)$ -, and $-NR^{48}S(O)_2$;

R^{53} and R^{55} are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino or cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the $-O$ - of lower alkoxy is fluoro;

R^{52} and R^{56} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy;

R^{49} is selected from the group consisting of hydrogen, lower alkyl, and fluoro substituted lower alkyl;

Cy is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R^{39} is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, aryl, heteroaryl, and $NR^{50}R^{51}$, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, and wherein aryl and heteroaryl are optionally substituted with one or more independent substituents R^{23} ;

R^{50} is hydrogen or lower alkyl optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino;

R^{51} is aryl or heteroaryl, wherein aryl and heteroaryl are optionally substituted with one or more independent substituents R^{23} ;

R^{23} at each occurrence is independently selected from the group consisting of $-OH$, $-NH_2$, $-CN$, $-NO_2$, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{57}$, $-SR^{57}$, $-NR^{48}R^{57}$, $-NR^{48}C(O)R^{57}$, $-NR^{48}S(O)_2R^{57}$, $-S(O)_2R^{57}$, $-C(O)R^{57}$, $-C(O)OR^{57}$, $-C(O)NR^{48}R^{57}$, $-S(O)_2NR^{48}R^{57}$, 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 R^{23} , or as substituents of lower alkyl, are optionally substituted with one or more substituents selected from the

group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -OR⁵⁸, -SR⁵⁸, -NR⁴⁸R⁵⁸, -NR⁴⁸C(O)R⁵⁸, -NR⁴⁸S(O)₂R⁵⁸, -S(O)₂R⁵⁸, -C(O)R⁵⁸, -C(O)OR⁵⁸, -C(O)NR⁴⁸R⁵⁸, -S(O)₂NR⁴⁸R⁵⁸, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; R⁵⁷ is 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, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of -OR⁵⁷, -SR⁵⁷, -NR⁴⁸R⁵⁷, -C(O)OR⁵⁷, -C(O)NR⁴⁸R⁵⁷, or -S(O)₂NR⁴⁸R⁵⁷ is fluoro, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R⁵⁷ or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -OR⁵⁸, -SR⁵⁸, -NR⁴⁸R⁵⁸, -NR⁴⁸C(O)R⁵⁸, -NR⁴⁸S(O)₂R⁵⁸, -S(O)₂R⁵⁸, -C(O)R⁵⁸, -C(O)OR⁵⁸, -C(O)NR⁴⁸R⁵⁸, -S(O)₂NR⁴⁸R⁵⁸, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

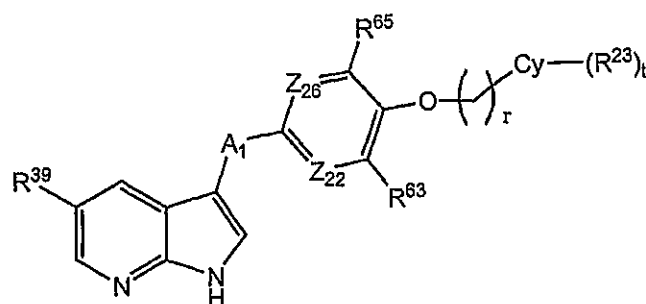
R⁵⁸ at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of -OR⁵⁸, -SR⁵⁸, -NR⁴⁸R⁵⁸, -C(O)OR⁵⁸, -C(O)NR⁴⁸R⁵⁸, or -S(O)₂NR⁴⁸R⁵⁸ is fluoro;

R⁴⁸ at each occurrence is independently hydrogen or lower alkyl; and

t is 0, 1, 2, or 3.

[0012] In some embodiments of compounds of Formula IIIb, A₁ is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-, more preferably -CH₂-. In some embodiments, A₁ is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-, more preferably -CH₂-, and R⁵³ and R⁵⁵ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments, L₃ is -NR⁴⁸CH(R⁴⁹)-, -SCH(R⁴⁹)-, or -OCH(R⁴⁹)-, preferably -OCH(R⁴⁹)-. In some embodiments, A₁ is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-, more preferably -CH₂-, and L₃ is -NR⁴⁸CH(R⁴⁹)-, -SCH(R⁴⁹)-, or -OCH(R⁴⁹)-, preferably -OCH(R⁴⁹)-.

[0013] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIp:



Formula IIIp

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A_1 is $-O-$, $-CR^{40}R^{41}-$, $-C(O)-$ or $-NR^{48}-$;

Z_{22} is N or CR^{62} ;

Z_{26} is N or CR^{66} ;

r is 0, 1, or 2;

R^{40} and R^{41} are independently selected from the group consisting of hydrogen, fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or R^{40} and R^{41} combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl, wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, $-OH$, $-NH_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

R^{62} , R^{63} , R^{65} and R^{66} are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the $-O-$ of lower alkoxy is fluoro;

Cy is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

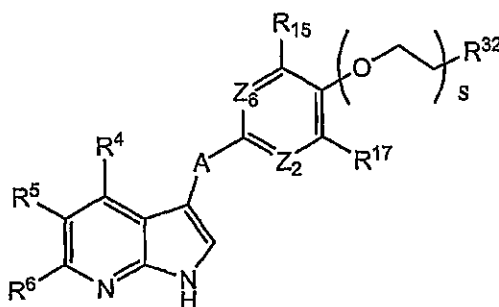
R^{39} is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, aryl, heteroaryl, and $NR^{50}R^{51}$, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, and wherein aryl and heteroaryl are optionally substituted with one or more independent substituents R^{23} ;

- R^{50} is hydrogen or lower alkyl optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino;
- R^{51} is aryl or heteroaryl, wherein aryl and heteroaryl are optionally substituted with one or more independent substituents R^{23} ;
- R^{23} at each occurrence is independently selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -OR⁵⁷, -SR⁵⁷, -NR⁴⁸R⁵⁷, -NR⁴⁸C(O)R⁵⁷, -NR⁴⁸S(O)₂R⁵⁷, -S(O)₂R⁵⁷, -C(O)R⁵⁷, -C(O)OR⁵⁷, -C(O)NR⁴⁸R⁵⁷, -S(O)₂NR⁴⁸R⁵⁷, 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 R^{23} , or as substituents of lower alkyl, are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -OR⁵⁸, -SR⁵⁸, -NR⁴⁸R⁵⁸, -NR⁴⁸C(O)R⁵⁸, -NR⁴⁸S(O)₂R⁵⁸, -S(O)₂R⁵⁸, -C(O)R⁵⁸, -C(O)OR⁵⁸, -C(O)NR⁴⁸R⁵⁸, -S(O)₂NR⁴⁸R⁵⁸, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;
- R^{57} is 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, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of -OR⁵⁷, -SR⁵⁷, -NR⁴⁸R⁵⁷, -C(O)OR⁵⁷, -C(O)NR⁴⁸R⁵⁷, or -S(O)₂NR⁴⁸R⁵⁷ is fluoro, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{57} or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -OR⁵⁸, -SR⁵⁸, -NR⁴⁸R⁵⁸, -NR⁴⁸C(O)R⁵⁸, -NR⁴⁸S(O)₂R⁵⁸, -S(O)₂R⁵⁸, -C(O)R⁵⁸, -C(O)OR⁵⁸, -C(O)NR⁴⁸R⁵⁸, -S(O)₂NR⁴⁸R⁵⁸, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;
- R^{58} 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, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of -OR⁵⁸, -SR⁵⁸, -NR⁴⁸R⁵⁸, -C(O)OR⁵⁸, -C(O)NR⁴⁸R⁵⁸, or -S(O)₂NR⁴⁸R⁵⁸ is fluoro;

R^{48} at each occurrence is independently hydrogen or lower alkyl; and
 t is 0, 1, 2, or 3.

[0014] In some embodiments of compounds of Formula IIIp, A_1 is $-CR^{40}R^{41}-$ or $-C(O)-$, preferably $-CH_2-$ or $-C(O)-$. In some embodiments, A_1 is $-CR^{40}R^{41}-$ or $-C(O)-$, preferably $-CH_2-$ or $-C(O)-$, and R^{62} , R^{64} , R^{65} and R^{66} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy.

[0015] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIc:



Formula IIIc

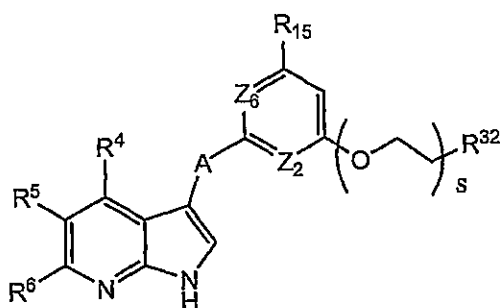
all salts, prodrugs, tautomers and isomers thereof, wherein A , s , Z_2 , Z_6 , R^4 , R^5 , R^6 , R^{15} , R^{17} , and R^{32} are as defined for Formula III.

[0016] In some embodiments of compounds of Formula IIIc, R^4 and R^6 are hydrogen, A is $-O-$, $-CR^aR^b-$, $-NR^1-$, or $-C(O)-$, preferably $-CH_2-$ or $-C(O)-$, more preferably $-CH_2-$, R^{17} is selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the $-O-$ of lower alkoxy is fluoro, and R^{15} is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy.

[0017] In some embodiments of compounds of Formula IIIc, R^4 and R^6 are hydrogen, A is $-O-$, $-CR^aR^b-$, $-NR^1-$, or $-C(O)-$, preferably $-CH_2-$ or $-C(O)-$, R^{17} is selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the $-O-$ of lower alkoxy is fluoro, R^{15} is selected from the

group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, Z_2 is N or CR^{12} , Z_6 is N or CR^{16} , R^{12} and R^{16} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, and R^5 is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, optionally substituted aryl, optionally substituted heteroaryl, and $-NR^{21}R^{22}$, wherein R^{21} is hydrogen or lower alkyl, and R^{22} is hydrogen, lower alkyl, optionally substituted aryl or optionally substituted heteroaryl, and wherein the alkyl chain of R^5 , R^{21} or R^{22} , when lower alkyl, or the alkyl chain of lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, further wherein R^{32} is optionally substituted lower alkyl or $-OR^{18}$, where R^{18} is as defined for Formula III.

[0018] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIIn:



Formula IIIIn

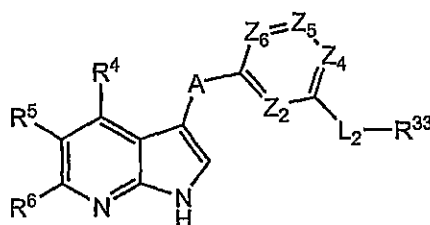
all salts, prodrugs, tautomers and isomers thereof, wherein A, s, Z_2 , Z_6 , R^4 , R^5 , R^6 , R^{15} , and R^{32} are as defined for Formula III.

[0019] In some embodiments of compounds of Formula IIIIn, R^4 and R^6 are hydrogen, A is $-O-$, $-CR^aR^b-$, $-NR^1-$, or $-C(O)-$, preferably $-CH_2-$ or $-C(O)-$, more preferably $-CH_2-$, and R^{15} is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy.

[0020] In some embodiments of compounds of Formula IIIIn, R^4 and R^6 are hydrogen, A is $-O-$, $-CR^aR^b-$, $-NR^1-$, or $-C(O)-$, preferably $-CH_2-$ or $-C(O)-$, R^{15} is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, Z_2 is N or CR^{12} , Z_6 is N or CR^{16} , R^{12} and R^{16} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, and R^5 is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, optionally substituted aryl, optionally substituted heteroaryl, and $-NR^{21}R^{22}$,

wherein R^{21} is hydrogen or lower alkyl, and R^{22} is hydrogen, lower alkyl, optionally substituted aryl or optionally substituted heteroaryl, and wherein the alkyl chain of R^5 , R^{21} or R^{22} , when lower alkyl, or the alkyl chain of lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, further wherein R^{32} is optionally substituted lower alkyl or -OR¹⁸, where R^{18} is as defined for Formula III.

[0021] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIo:



Formula IIIo

all salts, prodrugs, tautomers and isomers thereof, wherein A, L₂, Z₂, Z₄, Z₅, Z₆, R⁴, R⁵, R⁶, and R³³ are as defined for Formula III.

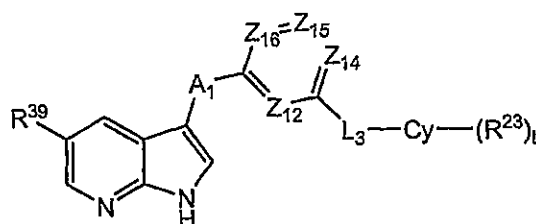
[0022] In some embodiments of compounds of Formula IIIo, R⁴ and R⁶ are hydrogen, A is -O-, -CR^aR^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, Z₂ is N or CR¹², Z₄ is N or CR¹⁴, Z₅ is N or CR¹⁵, Z₆ is N or CR¹⁶, and R¹², R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro.

[0023] In some embodiments of compounds of Formula IIIo, R⁴ and R⁶ are hydrogen, A is -O-, -CR^aR^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, Z₂ is N or CR¹², Z₄ is N or CR¹⁴, Z₅ is N or CR¹⁵, Z₆ is N or CR¹⁶, R¹², R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro, and R⁵ is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, optionally substituted aryl, optionally substituted heteroaryl, and NR²¹R²², wherein R²¹ is hydrogen or lower alkyl, and R²² is

hydrogen, lower alkyl, optionally substituted aryl or optionally substituted heteroaryl, and wherein the alkyl chain of R^5 , R^{21} or R^{22} , when lower alkyl, or the alkyl chain of lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino.

[0024] In some embodiments of compounds of Formula IIIo, R^4 and R^6 are hydrogen, A is -O-, -CR^aR^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, Z₂ is N or CR¹², Z₄ is N or CR¹⁴, Z₅ is N or CR¹⁵, Z₆ is N or CR¹⁶, R¹², R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, and R⁵ is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, optionally substituted aryl, optionally substituted heteroaryl, and NR²¹R²², wherein R²¹ is hydrogen or lower alkyl, and R²² is hydrogen, lower alkyl, optionally substituted aryl or optionally substituted heteroaryl, and wherein the alkyl chain of R^5 , R^{21} or R^{22} , when lower alkyl, or the alkyl chain of lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino.

[0025] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIq:



Formula IIIq

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A₁ is -O-, -CR⁴⁰R⁴¹-, -C(O)- or -NR⁴⁸-;

Z₁₂ is N or CR⁵²;

Z₁₄ is N or CR⁵⁴;

Z₁₅ is N or CR⁵⁵;

Z₁₆ is N or CR⁵⁶;

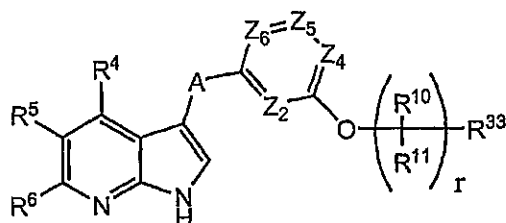
R⁴⁰ and R⁴¹ are independently selected from the group consisting of hydrogen, fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or

- R^{40} and R^{41} combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl, wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;
- L_3 is selected from the group consisting of -NR⁴⁸-, -S-, -O-, -NR⁴⁸CH(R⁴⁹)-, -SCH(R⁴⁹)-, -OCH(R⁴⁹)-, -C(O)NR⁴⁸-, -S(O)₂NR⁴⁸-, -CH(R⁴⁹)NR⁴⁸-, -CH(R⁴⁹)O-, -CH(R⁴⁹)S-, -NR⁴⁸C(O)-, and -NR⁴⁸S(O)₂-;
- R^{54} and R^{55} are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino or cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro;
- R^{52} and R^{56} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy;
- R^{49} is selected from the group consisting of hydrogen, lower alkyl, and fluoro substituted lower alkyl;
- Cy is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;
- R^{39} is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, aryl, heteroaryl, and NR⁵⁰R⁵¹, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, and wherein aryl and heteroaryl are optionally substituted with one or more independent substituents R²³;
- R^{50} is hydrogen or lower alkyl optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino;
- R^{51} is aryl or heteroaryl, wherein aryl and heteroaryl are optionally substituted with one or more independent substituents R²³;
- R^{23} at each occurrence is independently selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -OR⁵⁷, -SR⁵⁷, -NR⁴⁸R⁵⁷, -NR⁴⁸C(O)R⁵⁷, -NR⁴⁸S(O)₂R⁵⁷, -S(O)₂R⁵⁷, -C(O)R⁵⁷, -C(O)OR⁵⁷, -C(O)NR⁴⁸R⁵⁷, -S(O)₂NR⁴⁸R⁵⁷, 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 R^{23} , or as substituents of lower alkyl, are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -OR⁵⁸, -SR⁵⁸, -NR⁴⁸R⁵⁸, -NR⁴⁸C(O)R⁵⁸, -NR⁴⁸S(O)₂R⁵⁸, -S(O)₂R⁵⁸, -C(O)R⁵⁸, -C(O)OR⁵⁸, -C(O)NR⁴⁸R⁵⁸, -S(O)₂NR⁴⁸R⁵⁸, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; R^{57} is 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, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of -OR⁵⁷, -SR⁵⁷, -NR⁴⁸R⁵⁷, -C(O)OR⁵⁷, -C(O)NR⁴⁸R⁵⁷, or -S(O)₂NR⁴⁸R⁵⁷ is fluoro, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{57} or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -OR⁵⁸, -SR⁵⁸, -NR⁴⁸R⁵⁸, -NR⁴⁸C(O)R⁵⁸, -NR⁴⁸S(O)₂R⁵⁸, -S(O)₂R⁵⁸, -C(O)R⁵⁸, -C(O)OR⁵⁸, -C(O)NR⁴⁸R⁵⁸, -S(O)₂NR⁴⁸R⁵⁸, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; R^{58} 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, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of -OR⁵⁸, -SR⁵⁸, -NR⁴⁸R⁵⁸, -C(O)OR⁵⁸, -C(O)NR⁴⁸R⁵⁸, or -S(O)₂NR⁴⁸R⁵⁸ is fluoro; R^{48} at each occurrence is independently hydrogen or lower alkyl; and t is 0, 1, 2, or 3.

[0026] In some embodiments of compounds of Formula IIIq, A_1 is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-, more preferably -CH₂-. In some embodiments, A_1 is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-, more preferably -CH₂-, and R^{54} and R^{55} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. In some embodiments, L_3 is -NR⁴⁸CH(R⁴⁹)-, -SCH(R⁴⁹)-, or -OCH(R⁴⁹)-, preferably -OCH(R⁴⁹)-. In some embodiments, A_1 is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-, more preferably -CH₂-, and L_3 is -NR⁴⁸CH(R⁴⁹)-, -SCH(R⁴⁹)-, or -OCH(R⁴⁹)-, preferably -OCH(R⁴⁹)-.

[0027] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula III_d:



Formula III_d

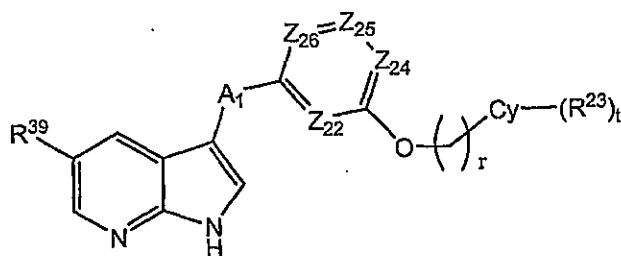
all salts, prodrugs, tautomers and isomers thereof, wherein A, Z₂, Z₄, Z₅, Z₆, R⁴, R⁵, R⁶, R¹⁰, R¹¹ and R³³ are as defined for Formula III, and r is 0, 1, or 2.

[0028] In some embodiments of compounds of Formula III_d, R⁴ and R⁶ are hydrogen, A is -O-, -CR^aR^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, Z₂ is N or CR¹², Z₄ is N or CR¹⁴, Z₅ is N or CR¹⁵, Z₆ is N or CR¹⁶, and R¹², R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro.

[0029] In some embodiments of compounds of Formula III_d, R⁴ and R⁶ are hydrogen, A is -O-, -CR^aR^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, Z₂ is N or CR¹², Z₄ is N or CR¹⁴, Z₅ is N or CR¹⁵, Z₆ is N or CR¹⁶, R¹², R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro, R¹⁰ and R¹¹ are independently selected from the group consisting of hydrogen, fluoro, lower alkyl, and fluoro substituted lower alkyl, and R⁵ is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, optionally substituted aryl, optionally substituted heteroaryl, and NR²¹R²², wherein R²¹ is hydrogen or lower alkyl, and R²² is hydrogen, lower alkyl, optionally substituted aryl or optionally substituted heteroaryl, and wherein the alkyl chain of R⁵, R²¹ or R²², when lower alkyl, or the alkyl chain of lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino.

[0030] In some embodiments of compounds of Formula III, R^4 and R^6 are hydrogen, A is -O-, -CR²R^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, Z₂ is N or CR¹², Z₄ is N or CR¹⁴, Z₅ is N or CR¹⁵, Z₆ is N or CR¹⁶, R¹², R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, R¹⁰ and R¹¹ are independently selected from the group consisting of hydrogen, fluoro, lower alkyl, and fluoro substituted lower alkyl, and R⁵ is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, optionally substituted aryl, optionally substituted heteroaryl, and NR²¹R²², wherein R²¹ is hydrogen or lower alkyl, and R²² is hydrogen, lower alkyl, optionally substituted aryl or optionally substituted heteroaryl, and wherein the alkyl chain of R⁵, R²¹ or R²², when lower alkyl, or the alkyl chain of lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino.

[0031] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIe:



Formula IIIe

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A₁ is -O-, -CR⁴⁰R⁴¹-, -C(O)- or -NR⁴⁸-;

Z₂₂ is N or CR⁶²;

Z₂₄ is N or CR⁶⁴;

Z₂₅ is N or CR⁶⁵;

Z₂₆ is N or CR⁶⁶;

r is 0, 1, or 2;

R⁴⁰ and R⁴¹ are independently selected from the group consisting of hydrogen, fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or R⁴⁰ and R⁴¹ combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl, wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl is optionally substituted with one or more substituents selected from the

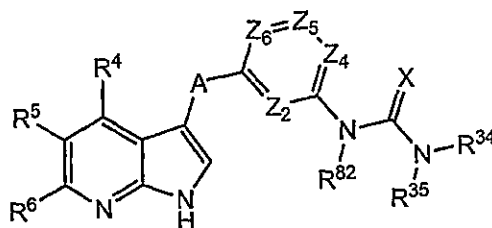
- group consisting of halogen, -OH, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;
- R⁶², R⁶⁴, R⁶⁵ and R⁶⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro;
- Cy is selected from the group consisting of aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;
- R³⁹ is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, aryl, heteroaryl, and NR⁵⁰R⁵¹, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, and wherein aryl and heteroaryl are optionally substituted with one or more independent substituents R²³;
- R⁵⁰ is hydrogen or lower alkyl optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino;
- R⁵¹ is aryl or heteroaryl, wherein aryl and heteroaryl are optionally substituted with one or more independent substituents R²³;
- R²³ at each occurrence is independently selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -OR⁵⁷, -SR⁵⁷, -NR⁴⁸R⁵⁷, -NR⁴⁸C(O)R⁵⁷, -NR⁴⁸S(O)₂R⁵⁷, -S(O)₂R⁵⁷, -C(O)R⁵⁷, -C(O)OR⁵⁷, -C(O)NR⁴⁸R⁵⁷, -S(O)₂NR⁴⁸R⁵⁷, 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 R²³, or as substituents of lower alkyl, are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -OR⁵⁸, -SR⁵⁸, -NR⁴⁸R⁵⁸, -NR⁴⁸C(O)R⁵⁸, -NR⁴⁸S(O)₂R⁵⁸, -S(O)₂R⁵⁸, -C(O)R⁵⁸, -C(O)OR⁵⁸, -C(O)NR⁴⁸R⁵⁸, -S(O)₂NR⁴⁸R⁵⁸, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;
- R⁵⁷ is 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,

R^{58} 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, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of $-OR^{58}$, $-SR^{58}$, $-NR^{48}R^{58}$, $-C(O)OR^{58}$, $-C(O)NR^{48}R^{58}$, or $-S(O)_2NR^{48}R^{58}$ is fluoro;

R^{48} at each occurrence is independently hydrogen or lower alkyl; and

t is 0, 1, 2, or 3.

[0033] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIf:



Formula IIIf

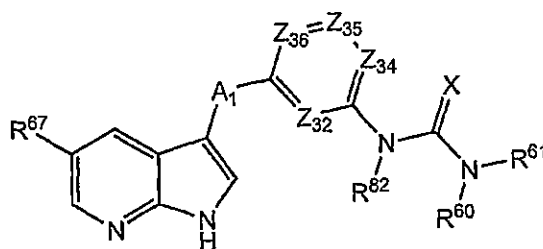
all salts, prodrugs, tautomers and isomers thereof, wherein A, Z₂, Z₄, Z₅, Z₆, X, R⁴, R⁵, R⁶, R³⁴, R³⁵ and R⁸² are as defined for Formula III.

[0034] In some embodiments of compounds of Formula IIIf, R⁴ and R⁶ are hydrogen, A is -O-, -CR^aR^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, Z₂ is N or CR¹², Z₄ is N or CR¹⁴, Z₅ is N or CR¹⁵, Z₆ is N or CR¹⁶, and R¹², R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting

of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro.

[0035] In some embodiments of compounds of Formula IIIf, R⁴ and R⁶ are hydrogen, A is -O-, -CR^aR^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, Z₂ is N or CR¹², Z₄ is N or CR¹⁴, Z₅ is N or CR¹⁵, Z₆ is N or CR¹⁶, R¹², R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro, and one of R³⁴ and R³⁵ is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl, and the other of R³⁴ and R³⁵ is hydrogen or lower alkyl, or R³⁴ and R³⁵ together with the nitrogen to which they are attached form optionally substituted 5-7 membered heterocycloalkyl or optionally substituted 5 or 7 membered nitrogen containing heteroaryl.

[0036] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIg:



Formula IIIg

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A₁ is -O-, -CR⁴⁰R⁴¹-, -C(O)- or -NR⁴⁸-;

Z₃₂ is N or CR⁷²;

Z₃₄ is N or CR⁷⁴;

Z₃₅ is N or CR⁷⁵;

Z₃₆ is N or CR⁷⁶;

X is O or S;

R⁴⁸ at each occurrence is independently hydrogen or lower alkyl;

R^{40} and R^{41} are independently selected from the group consisting of hydrogen, fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or R^{40} and R^{41} combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl, wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

R^{72} , R^{74} , R^{75} and R^{76} are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl and lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the -O- of lower alkoxy is fluoro;

R^{67} is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -C(S)NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)OR⁶⁸, -C(O)NR⁶⁹R⁶⁸, -C(S)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹C(S)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -NR⁶⁹C(O)NH₂, -NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸, -NR⁶⁹S(O)₂NH₂, -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, and -S(O)₂R⁶⁸;

one of R^{60} and R^{61} is lower alkyl, fluoro substituted lower alkyl, or -(CH₂)₀₋₂R⁷⁰, and the other of R^{60} and R^{61} is hydrogen or lower alkyl;

or R^{60} and R^{61} together with the nitrogen to which they are attached form optionally substituted 5-7 membered heterocycloalkyl or optionally substituted 5 or 7 membered nitrogen containing heteroaryl;

R^{68} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that when R^{68} is optionally substituted lower alkenyl, no alkene carbon thereof is bound to N, S, O, S(O), S(O)₂, C(O) or C(S) of -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)OR⁶⁸, -C(O)NR⁶⁹R⁶⁸, -C(S)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹C(S)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -NR⁶⁹C(O)NH₂, -NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸, -NR⁶⁹S(O)₂NH₂, -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, or -S(O)₂R⁶⁸, optionally substituted lower alkynyl, provided, however, that when R^{68} is optionally substituted lower alkynyl, no alkyne carbon thereof is bound to N, S, O, S(O), S(O)₂, C(O) or C(S) of -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸,

-C(O)OR⁶⁸, -C(O)NR⁶⁹R⁶⁸, -C(S)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹C(S)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -NR⁶⁹C(O)NH₂, -NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸, -NR⁶⁹S(O)₂NH₂, -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, or -S(O)₂R⁶⁸, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R⁶⁹ is hydrogen or optionally substituted lower alkyl;

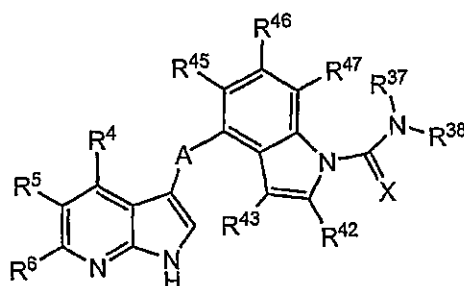
R⁷⁰ is selected from the group consisting of optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R⁸² is hydrogen or lower alkyl.

[0037] In some embodiments of compounds of Formula IIIg, A₁ is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-.

[0038] In some embodiments of compounds of Formula IIIg, A₁ is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-, and R⁶⁷ is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -CN, -S(O)₂NH₂, -C(O)NH₂, -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -S(O)R⁶⁸, and -S(O)₂R⁶⁸.

[0039] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIh:



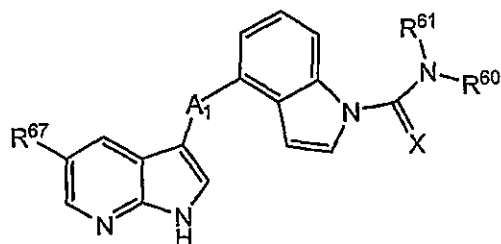
Formula IIIh

all salts, prodrugs, tautomers and isomers thereof, wherein A, X, R⁴, R⁵, R⁶, R³⁷, R³⁸, R⁴², R⁴³, R⁴⁵, R⁴⁶, and R⁴⁷ are as defined for Formula III.

[0040] In some embodiments of compounds of Formula IIIh, R⁴ and R⁶ are hydrogen, A is -O-, -CR^aR^b-, -NR¹-, or -C(O)-, preferably -CH₂- or -C(O)-, and R⁴², R⁴³, R⁴⁵, R⁴⁶ and R⁴⁷ are independently selected from the group consisting of hydrogen, halogen, -OH, -CN, -NO₂, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkyl, mono-alkylamino, di-alkylamino, and cycloalkylamino, further

wherein at least one of, at least two of, at least three of, at least four of, or preferably all of R^{42} , R^{43} , R^{45} , R^{46} and R^{47} are hydrogen.

[0041] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIi:



Formula IIIi

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

A_1 is -O-, $-CR^{40}R^{41}-$, $-C(O)-$ or $-NR^{48}-$;

X is O or S;

R^{48} at each occurrence is independently hydrogen or lower alkyl;

R^{40} and R^{41} are independently selected from the group consisting of hydrogen, fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or

R^{40} and R^{41} combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl, wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

R^{67} is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, -NH₂, -CN, -NO₂, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^{68}$, $-SR^{68}$, $-NR^{69}R^{68}$, $-C(O)R^{68}$, $-C(S)R^{68}$, $-C(O)OR^{68}$, $-C(O)NR^{69}R^{68}$, $-C(S)NR^{69}R^{68}$, $-S(O)_2NR^{69}R^{68}$, $-NR^{69}C(O)R^{68}$, $-NR^{69}C(S)R^{68}$, $-NR^{69}S(O)_2R^{68}$, $-NR^{69}C(O)NH_2$, $-NR^{69}C(O)NR^{69}R^{68}$, $-NR^{69}C(S)NH_2$, $-NR^{69}C(S)NR^{69}R^{68}$, $-NR^{69}S(O)_2NH_2$, $-NR^{69}S(O)_2NR^{69}R^{68}$, $-S(O)R^{68}$, and $-S(O)_2R^{68}$;

one of R^{60} and R^{61} is lower alkyl, fluoro substituted lower alkyl, or $-(CH_2)_{0-2}R^{70}$ and the other of R^{60} and R^{61} is hydrogen or lower alkyl;

or R⁶⁰ and R⁶¹ together with the nitrogen to which they are attached form optionally substituted 5-7 membered heterocycloalkyl or optionally substituted 5 or 7 membered nitrogen containing heteroaryl;

R⁶⁸ is selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that when R⁶⁸ is optionally substituted lower alkenyl, no alkene carbon thereof is bound to N, S, O, S(O), S(O)₂, C(O) or C(S) of -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)OR⁶⁸, -C(O)NR⁶⁹R⁶⁸, -C(S)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹C(S)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -NR⁶⁹C(O)NH₂, -NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸, -NR⁶⁹S(O)₂NH₂, -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, or -S(O)₂R⁶⁸, optionally substituted lower alkynyl, provided, however, that when R⁶⁸ is optionally substituted lower alkynyl, no alkyne carbon thereof is bound to N, S, O, S(O), S(O)₂, C(O) or C(S) of -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)OR⁶⁸, -C(O)NR⁶⁹R⁶⁸, -C(S)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹C(S)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -NR⁶⁹C(O)NH₂, -NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸, -NR⁶⁹S(O)₂NH₂, -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, or -S(O)₂R⁶⁸, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R⁶⁹ is hydrogen or optionally substituted lower alkyl; and

R⁷⁰ is selected from the group consisting of optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl.

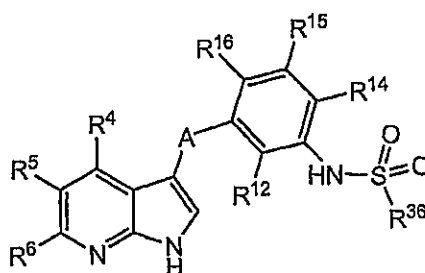
[0042] In some embodiments of compounds of Formula IIIi, A₁ is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-.

[0043] In some embodiments of compounds of Formula IIIi, A₁ is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-, and R⁶⁷ is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -CN, -S(O)₂NH₂, -C(O)NH₂, -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -S(O)R⁶⁸, and -S(O)₂R⁶⁸.

[0044] In some embodiments of compounds of Formula IIIi, A₁ is -CR⁴⁰R⁴¹- or -C(O)-, preferably -CH₂- or -C(O)-, more preferably -C(O)-, R⁶⁷ is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, optionally substituted aryl, optionally substituted heteroaryl, and NR²¹R²², wherein R²¹ is hydrogen or lower alkyl, and R²² is hydrogen, lower alkyl, optionally substituted aryl or optionally substituted heteroaryl, and wherein the alkyl chain of R⁶⁷, R²¹ or R²², when lower alkyl, or the alkyl chain of lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted

lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, and one of R^{60} and R^{61} is lower alkyl or fluoro substituted lower alkyl, and the other of R^{60} and R^{61} is hydrogen or lower alkyl. In some embodiments, A_1 is $-C(O)-$, R^{67} is optionally substituted aryl or optionally substituted heteroaryl, and one of R^{60} and R^{61} is lower alkyl or fluoro substituted lower alkyl, and the other of R^{60} and R^{61} is hydrogen or lower alkyl.

[0045] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIj:



Formula IIIj

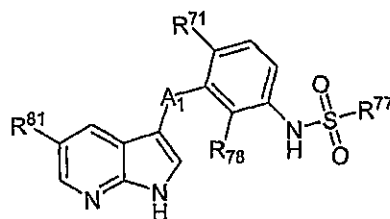
all salts, prodrugs, tautomers and isomers thereof, wherein A, R^4 , R^5 , R^6 , R^{12} , R^{14} , R^{15} , R^{16} , and R^{36} are as defined for Formula III.

[0046] In some embodiments of compounds of Formula IIIj, R^4 and R^6 are hydrogen, A is $-O-$, $-CR^aR^b-$, $-NR^1-$, or $-C(O)-$, preferably $-CH_2-$ or $-C(O)-$, and R^{12} , R^{14} , R^{15} and R^{16} are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the $-O-$ of lower alkoxy is fluoro, preferably wherein R^{14} and R^{15} are hydrogen, more preferably wherein R^{12} is fluoro, R^{16} is hydrogen, fluoro or chloro, and R^{14} and R^{15} are hydrogen.

[0047] In some embodiments of compounds of Formula IIIj, R^4 and R^6 are hydrogen, A is $-O-$, $-CR^aR^b-$, $-NR^1-$, or $-C(O)-$, preferably $-CH_2-$ or $-C(O)-$, R^{12} , R^{14} , R^{15} and R^{16} are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, wherein the alkyl chain of lower alkyl or lower alkoxy is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided, however, that any substitution on the alkyl carbon bound to the $-O-$ of lower alkoxy is fluoro, preferably wherein R^{14} and R^{15} are hydrogen, more preferably wherein R^{12} is fluoro, R^{16} is hydrogen, fluoro or chloro, and R^{14} and R^{15} are hydrogen, and R^{36} is selected from the group consisting of optionally substituted C_{2-6} alkyl, optionally substituted cycloalkyl, optionally

substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and $-NR^{19}R^{20}$, where R^{19} and R^{20} are as defined for Formula III, further wherein one of R^{19} and R^{20} is hydrogen or optionally substituted lower alkyl, and the other of R^{19} and R^{20} is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl.

[0048] In some embodiments, compounds of Formula III have the structure according to the following sub-generic structure Formula IIIk:



Formula IIIk

all salts, prodrugs, tautomers and isomers thereof,

wherein:

A_1 is $-O-$, $-CR^{40}R^{41}-$, $-C(O)-$ or $-NR^{48}-$;

R^{81} is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-OH$, $-NH_2$, $-CN$, $-NO_2$, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^{68}$, $-SR^{68}$, $-NR^{69}R^{68}$, $-C(O)R^{68}$, $-C(S)R^{68}$, $-C(O)OR^{68}$, $-C(O)NR^{69}R^{68}$, $-C(S)NR^{69}R^{68}$, $-S(O)_2NR^{69}R^{68}$, $-NR^{69}C(O)R^{68}$, $-NR^{69}C(S)R^{68}$, $-NR^{69}S(O)_2R^{68}$, $-NR^{69}C(O)NH_2$, $-NR^{69}C(O)NR^{69}R^{68}$, $-NR^{69}C(S)NH_2$, $-NR^{69}C(S)NR^{69}R^{68}$, $-NR^{69}S(O)_2NH_2$, $-NR^{69}S(O)_2NR^{69}R^{68}$, $-S(O)R^{68}$, and $-S(O)_2R^{68}$;

R^{71} and R^{78} are independently selected from the group consisting of hydrogen, halogen, C_{1-3} alkyl, and fluoro substituted C_{1-3} alkyl;

R^{77} is selected from the group consisting of substituted methyl, optionally substituted C_{2-6} alkyl, optionally substituted aryl, optionally substituted heteroaryl, and $-NR^{79}R^{80}$, wherein methyl is substituted with one or more substituents selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl;

R^{68} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that when R^{68} is optionally substituted lower alkenyl, no alkene carbon thereof is bound to N, S, O, $S(O)$, $S(O)_2$, $C(O)$ or $C(S)$ of $-OR^{68}$, $-SR^{68}$, $-NR^{69}R^{68}$, $-C(O)R^{68}$, $-C(S)R^{68}$, $-C(O)OR^{68}$, $-C(O)NR^{69}R^{68}$, $-C(S)NR^{69}R^{68}$, $-S(O)_2NR^{69}R^{68}$, $-NR^{69}C(O)R^{68}$, $-NR^{69}C(S)R^{68}$, $-NR^{69}S(O)_2R^{68}$, $-NR^{69}C(O)NH_2$,

-NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸, -NR⁶⁹S(O)₂NH₂,
 -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, or -S(O)₂R⁶⁸, optionally substituted lower alkynyl, provided,
 however, that when R⁶⁸ is optionally substituted lower alkynyl, no alkyne carbon thereof is
 bound to N, S, O, S(O), S(O)₂, C(O) or C(S) of -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸,
 -C(O)OR⁶⁸, -C(O)NR⁶⁹R⁶⁸, -C(S)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹C(S)R⁶⁸,
 -NR⁶⁹S(O)₂R⁶⁸, -NR⁶⁹C(O)NH₂, -NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸,
 -NR⁶⁹S(O)₂NH₂, -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, or -S(O)₂R⁶⁸, optionally substituted
 cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally
 substituted heteroaryl;

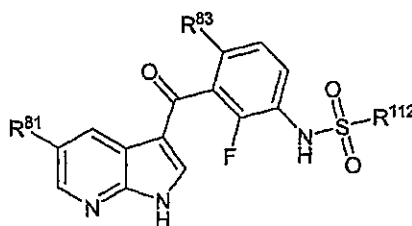
R⁶⁹ is hydrogen or optionally substituted lower alkyl; and

R⁷⁹ and R⁸⁰ are independently hydrogen or optionally substituted lower alkyl, or R⁷⁹ and R⁸⁰
 combine with the nitrogen to which they are attached to form optionally substituted 5-7
 membered heterocycloalkyl.

[0049] In some embodiments of compounds of Formula IIIk, A₁ is -CR⁴⁰R⁴¹- or -C(O)-, preferably
 -CH₂- or -C(O)-, more preferably -C(O)-.

[0050] In some embodiments of compounds of Formula IIIk, A₁ is -CR⁴⁰R⁴¹- or -C(O)-, preferably
 -CH₂- or -C(O)-, more preferably -C(O)-, and R⁸¹ is selected from the group consisting of hydrogen,
 halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally
 substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl,
 optionally substituted aryl, optionally substituted heteroaryl, -CN, -S(O)₂NH₂, -C(O)NH₂, -OR⁶⁸,
 -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸,
 -S(O)R⁶⁸, and -S(O)₂R⁶⁸.

[0051] In some embodiments, compounds of Formula III have the structure according to the
 following sub-generic structure Formula IIIIm:



Formula IIIIm

all salts, prodrugs, tautomers and isomers thereof,

wherein:

R⁸¹ is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl,
 optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally
 substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl,

optionally substituted heteroaryl, -OH, -NH₂, -CN, -NO₂, -C(O)OH, -S(O)₂NH₂, -C(O)NH₂, -C(S)NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)OR⁶⁸, -C(O)NR⁶⁹R⁶⁸, -C(S)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹C(S)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -NR⁶⁹C(O)NH₂, -NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸, -NR⁶⁹S(O)₂NH₂, -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, and -S(O)₂R⁶⁸;

R⁸³ is selected from the group consisting of hydrogen, fluoro and chloro;

R¹¹² is selected from the group consisting of optionally substituted C₂₋₆ alkyl, optionally substituted aryl, optionally substituted heteroaryl, and -NR⁷⁹R⁸⁰;

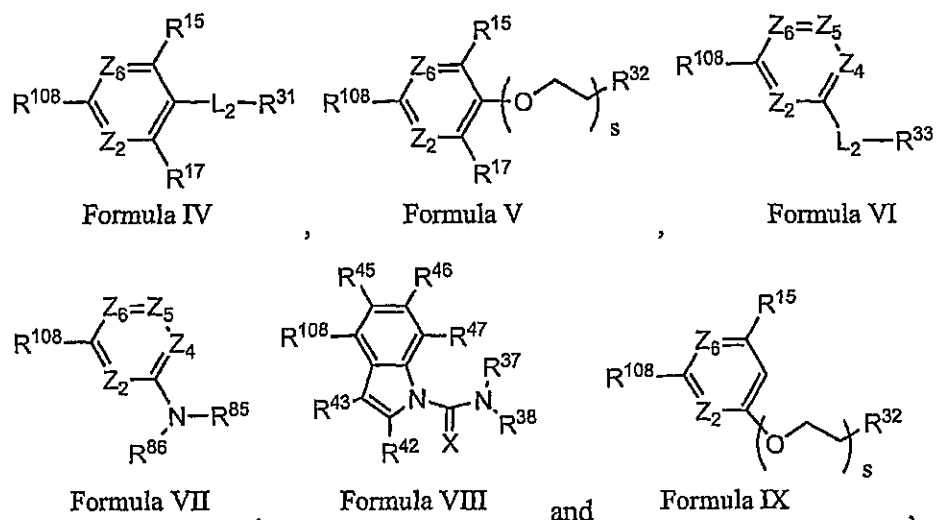
R⁶⁸ is selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that when R⁶⁸ is optionally substituted lower alkenyl, no alkene carbon thereof is bound to N, S, O, S(O), S(O)₂, C(O) or C(S) of -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)OR⁶⁸, -C(O)NR⁶⁹R⁶⁸, -C(S)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹C(S)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -NR⁶⁹C(O)NH₂, -NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸, -NR⁶⁹S(O)₂NH₂, -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, or -S(O)₂R⁶⁸, optionally substituted lower alkynyl, provided, however, that when R⁶⁸ is optionally substituted lower alkynyl, no alkyne carbon thereof is bound to N, S, O, S(O), S(O)₂, C(O) or C(S) of -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)OR⁶⁸, -C(O)NR⁶⁹R⁶⁸, -C(S)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹C(S)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -NR⁶⁹C(O)NH₂, -NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸, -NR⁶⁹S(O)₂NH₂, -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, or -S(O)₂R⁶⁸, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R⁶⁹ is selected from the group consisting of hydrogen and optionally substituted lower alkyl; and R⁷⁹ and R⁸⁰ are independently hydrogen or optionally substituted lower alkyl, or R⁷⁹ and R⁸⁰ combine with the nitrogen to which they are attached to form optionally substituted 5-7 membered heterocycloalkyl.

[0052] In some embodiments of compounds of Formula III_m, R⁸¹ is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -CN, -S(O)₂NH₂, -C(O)NH₂, -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -S(O)R⁶⁸, and -S(O)₂R⁶⁸.

[0053] In one aspect, the present invention includes compounds that are useful as intermediates in the preparation of compounds of Formula III, the compounds having a structure selected from the

group consisting of Formula IV, Formula V, Formula VI, Formula VII, Formula VIII, and Formula IX as follows:



wherein:

$Z_2, Z_4, Z_5, Z_6, L_2, X, s, R^{15}, R^{17}, R^{31}, R^{32}, R^{33}, R^{37}, R^{38}, R^{42}, R^{43}, R^{45}, R^{46},$ and R^{47} are as defined for Formula III;

R^{108} is selected from the group consisting of $-C(O)R^{84}, -CH_2I, -CH_2Cl, -CH_2Br, -CH_2OH,$ and $-CH_2OS(O)_2R^{109};$

R^{109} is selected from the group consisting of lower alkyl and aryl;

R^{84} is selected from the group consisting of hydrogen, lower alkoxy, $-OH,$ and $-Cl;$

R^{85} is selected from the group consisting of hydrogen, a nitrogen protecting group, $-S(O)_2R^{87}, -C(O)NR^{88}R^{89},$ and $-C(S)NR^{88}R^{89};$

R^{86} is selected from the group consisting of hydrogen, lower alkyl, and a nitrogen protecting group;

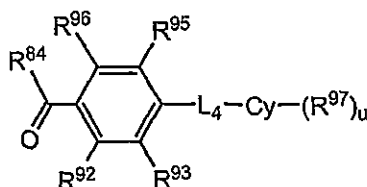
R^{87} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that when R^{87} is optionally substituted lower alkenyl, no alkene carbon thereof is bound to $S(O)_2,$ optionally substituted lower alkynyl, provided, however, that when R^{87} is optionally substituted lower alkynyl, no alkyne carbon thereof is bound to $S(O)_2,$ optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and $-NR^{90}R^{91};$ and

R^{88}, R^{89}, R^{90} and R^{91} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl; or

R^{88} and R^{89} together with the nitrogen to which they are attached form optionally substituted 5-7 membered heterocycloalkyl or optionally substituted 5 or 7 membered nitrogen containing heteroaryl.

[0054] In some embodiments of compounds of Formulae IV, V, VI, VII, or VIII, R^{108} is $-C(O)R^{84}$, preferably wherein R^{84} is hydrogen. In some embodiments of compounds of Formulae IV, V, VI, VII, or VIII, Z_2 is N or CR^{12} , Z_4 is N or CR^{14} , Z_5 is N or CR^{15} , and Z_6 is N or CR^{16} and R^{12} , R^{14} , R^{15} , R^{16} , R^{17} , R^{42} , R^{43} , R^{45} , R^{46} and R^{47} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy.

[0055] In some embodiments, compounds of Formula IV have the structure according to the following sub-generic structure Formula IVa:



Formula IVa

wherein:

R^{84} is selected from the group consisting of hydrogen, lower alkoxy, $-OH$, and $-Cl$;

R^{92} , R^{93} , R^{95} , and R^{96} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy;

L_4 is selected from the group consisting of $-NR^{48}-$, $-S-$, $-O-$, $-NR^{48}CH(R^{49})-$, $-SCH(R^{49})-$, $-OCH(R^{49})-$, $-C(O)NR^{48}-$, $-S(O)_2NR^{48}-$, $-CH(R^{49})NR^{48}-$, $-CH(R^{49})O-$, $-CH(R^{49})S-$, $-NR^{48}C(O)-$, and $-NR^{48}S(O)_2-$;

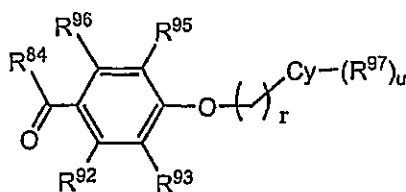
Cy is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

R^{97} at each occurrence is independently selected from the group consisting of $-OH$, $-NH_2$, $-CN$, $-NO_2$, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{57}$, $-SR^{57}$, $-NR^{48}R^{57}$, $-NR^{48}C(O)R^{57}$, $-NR^{48}S(O)_2R^{57}$, $-S(O)_2R^{57}$, $-C(O)R^{57}$, $-C(O)OR^{57}$, $-C(O)NR^{48}R^{57}$, $-S(O)_2NR^{48}R^{57}$, 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 R^{97} , or as substituents of lower alkyl, are optionally substituted with one or more substituents selected from the group consisting of $-OH$, $-NH_2$, $-CN$, $-NO_2$, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{58}$, $-SR^{58}$,

$-\text{NR}^{48}\text{R}^{58}$, $-\text{NR}^{48}\text{C}(\text{O})\text{R}^{58}$, $-\text{NR}^{48}\text{S}(\text{O})_2\text{R}^{58}$, $-\text{S}(\text{O})_2\text{R}^{58}$, $-\text{C}(\text{O})\text{R}^{58}$, $-\text{C}(\text{O})\text{OR}^{58}$, $-\text{C}(\text{O})\text{NR}^{48}\text{R}^{58}$,
 $-\text{S}(\text{O})_2\text{NR}^{48}\text{R}^{58}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;
 R^{49} is selected from the group consisting of hydrogen, lower alkyl, and fluoro substituted lower alkyl;
 R^{57} is 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, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of $-\text{OR}^{57}$, $-\text{SR}^{57}$, $-\text{NR}^{48}\text{R}^{57}$, $-\text{C}(\text{O})\text{OR}^{57}$, $-\text{C}(\text{O})\text{NR}^{48}\text{R}^{57}$, or $-\text{S}(\text{O})_2\text{NR}^{48}\text{R}^{57}$ is fluoro, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{57} or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of $-\text{OH}$, $-\text{NH}_2$, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{S}(\text{O})_2\text{NH}_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OR}^{58}$, $-\text{SR}^{58}$, $-\text{NR}^{48}\text{R}^{58}$, $-\text{NR}^{48}\text{C}(\text{O})\text{R}^{58}$, $-\text{NR}^{48}\text{S}(\text{O})_2\text{R}^{58}$, $-\text{S}(\text{O})_2\text{R}^{58}$, $-\text{C}(\text{O})\text{R}^{58}$, $-\text{C}(\text{O})\text{OR}^{58}$, $-\text{C}(\text{O})\text{NR}^{48}\text{R}^{58}$, $-\text{S}(\text{O})_2\text{NR}^{48}\text{R}^{58}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and
 R^{58} 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, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of $-\text{OR}^{58}$, $-\text{SR}^{58}$, $-\text{NR}^{48}\text{R}^{58}$, $-\text{C}(\text{O})\text{OR}^{58}$, $-\text{C}(\text{O})\text{NR}^{48}\text{R}^{58}$, or $-\text{S}(\text{O})_2\text{NR}^{48}\text{R}^{58}$ is fluoro;
 R^{48} at each occurrence is independently hydrogen or lower alkyl; and
 u is 0, 1, 2, or 3.

[0056] In some embodiments of compounds of Formula IVa, at least two of R^{92} , R^{93} , R^{95} and R^{96} are hydrogen. In some embodiments, at least two of R^{92} , R^{93} , R^{95} and R^{96} are hydrogen, L_4 is $-\text{NR}^{48}\text{CH}(\text{R}^{49})-$, $-\text{SCH}(\text{R}^{49})-$, or $-\text{OCH}(\text{R}^{49})-$, preferably L_4 is $-\text{OCH}_2-$, Cy is aryl or heteroaryl, and each R^{97} is independently selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy.

[0057] In some embodiments, compounds of Formula IV have the structure according to the following sub-generic structure Formula IVb:

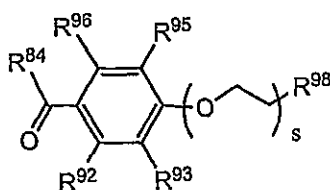


Formula IVb

wherein R^{84} , R^{92} , R^{93} , R^{95} , R^{96} , R^{97} , Cy and u are as defined for Formula IVa, and r is 0, 1 or 2.

[0058] In some embodiments of compounds of Formula IVb, at least two of R^{92} , R^{93} , R^{95} and R^{96} are hydrogen. In some embodiments, at least two of R^{92} , R^{93} , R^{95} and R^{96} are hydrogen, Cy is aryl or heteroaryl, and each R^{97} is independently selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy.

[0059] In some embodiments, compounds of Formula V have the structure according to the following sub-generic structure Formula Va:



Formula Va

wherein:

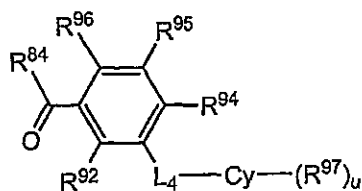
R^{84} is selected from the group consisting of hydrogen, lower alkoxy, -OH, and -Cl;

R^{92} , R^{93} , R^{95} , and R^{96} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy;

R^{98} is selected from the group consisting of hydrogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and

s is 0, 1, or 2;

[0060] In some embodiments, compounds of Formula VI have the structure according to the following sub-generic structure Formula VIa:



Formula VIa

wherein:

R^{84} is selected from the group consisting of hydrogen, lower alkoxy, -OH, and -Cl;

R^{92} , R^{94} , R^{95} , and R^{96} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy;

L_4 is selected from the group consisting of $-NR^{48}-$, $-S-$, $-O-$, $-NR^{48}CH(R^{49})-$, $-SCH(R^{49})-$, $-OCH(R^{49})-$, $-C(O)NR^{48}-$, $-S(O)_2NR^{48}-$, $-CH(R^{49})NR^{48}-$, $-CH(R^{49})O-$, $-CH(R^{49})S-$, $-NR^{48}C(O)-$, and $-NR^{48}S(O)_2-$;

Cy is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

R^{97} at each occurrence is independently selected from the group consisting of $-OH$, $-NH_2$, $-CN$, $-NO_2$, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{57}$, $-SR^{57}$, $-NR^{48}R^{57}$, $-NR^{48}C(O)R^{57}$, $-NR^{48}S(O)_2R^{57}$, $-S(O)_2R^{57}$, $-C(O)R^{57}$, $-C(O)OR^{57}$, $-C(O)NR^{48}R^{57}$, $-S(O)_2NR^{48}R^{57}$, 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 R^{97} , or as substituents of lower alkyl, are optionally substituted with one or more substituents selected from the group consisting of $-OH$, $-NH_2$, $-CN$, $-NO_2$, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{58}$, $-SR^{58}$, $-NR^{48}R^{58}$, $-NR^{48}C(O)R^{58}$, $-NR^{48}S(O)_2R^{58}$, $-S(O)_2R^{58}$, $-C(O)R^{58}$, $-C(O)OR^{58}$, $-C(O)NR^{48}R^{58}$, $-S(O)_2NR^{48}R^{58}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

R^{49} is selected from the group consisting of hydrogen, lower alkyl, and fluoro substituted lower alkyl;

R^{57} is 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, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of $-OR^{57}$, $-SR^{57}$, $-NR^{48}R^{57}$, $-C(O)OR^{57}$, $-C(O)NR^{48}R^{57}$, or $-S(O)_2NR^{48}R^{57}$ is fluoro, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{57} or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of $-OH$, $-NH_2$, $-CN$, $-NO_2$, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^{58}$, $-SR^{58}$, $-NR^{48}R^{58}$, $-NR^{48}C(O)R^{58}$, $-NR^{48}S(O)_2R^{58}$, $-S(O)_2R^{58}$, $-C(O)R^{58}$, $-C(O)OR^{58}$, $-C(O)NR^{48}R^{58}$, $-S(O)_2NR^{48}R^{58}$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

R^{58} 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, provided, however, that any substitution of

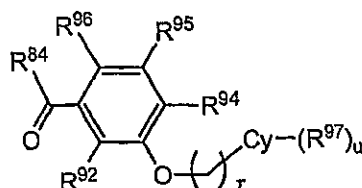
the alkyl carbon bound to O, S, or N of $-OR^{58}$, $-SR^{58}$, $-NR^{48}R^{58}$, $-C(O)OR^{58}$, $-C(O)NR^{48}R^{58}$, or $-S(O)_2NR^{48}R^{58}$ is fluoro;

R^{48} at each occurrence is independently hydrogen or lower alkyl; and

u is 0, 1, 2 or 3.

[0061] In some embodiments of compounds of Formula VIa, at least two of R^{92} , R^{94} , R^{95} and R^{96} are hydrogen. In some embodiments, at least two of R^{92} , R^{94} , R^{95} and R^{96} are hydrogen, L_4 is $-NR^{48}CH(R^{49})-$, $-SCH(R^{49})-$, or $-OCH(R^{49})-$, preferably L_4 is $-OCH_2-$, Cy is aryl or heteroaryl, and each R^{97} is independently selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy.

[0062] In some embodiments, compounds of Formula VI have the structure according to the following sub-generic structure Formula VIb:

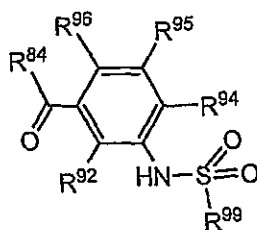


Formula VIb

wherein R^{84} , R^{92} , R^{94} , R^{95} , R^{96} , R^{97} , Cy and u are as defined for Formula VIa and r is 0, 1 or 2.

[0063] In some embodiments of compounds of Formula VIb, at least two of R^{92} , R^{94} , R^{95} and R^{96} are hydrogen. In some embodiments, at least two of R^{92} , R^{94} , R^{95} and R^{96} are hydrogen, Cy is aryl or heteroaryl, and each R^{97} is independently selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy.

[0064] In some embodiments, compounds of Formula VII have the structure according to the following sub-generic structure Formula VIIa:



Formula VIIa

wherein:

R^{84} is selected from the group consisting of hydrogen, lower alkoxy, $-OH$, and $-Cl$;

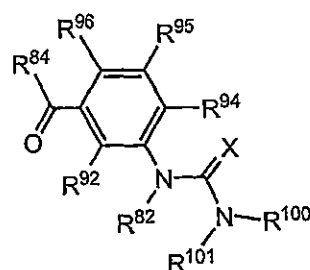
R^{92} , R^{94} , R^{95} , and R^{96} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy;

R^{99} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, and $-NR^{79}R^{80}$; and
 R^{79} and R^{80} are independently hydrogen or optionally substituted lower alkyl, or R^{79} and R^{80} combine with the nitrogen to which they are attached to form optionally substituted 5-7 membered heterocycloalkyl.

[0065] In some embodiments of compounds of Formula VIIa, one of R^{92} and R^{96} is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy, and the other of R^{92} and R^{96} is selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; in further embodiments, one of R^{92} and R^{96} is hydrogen, fluoro or chloro, and the other of R^{92} and R^{96} is fluoro or chloro; in further embodiments, R^{92} is fluoro and R^{96} is hydrogen, fluoro, or chloro; in further embodiments, R^{92} and R^{96} are both fluoro.

[0066] In some embodiments of compounds of Formula VIIa, R^{94} and R^{95} are hydrogen; in further embodiments, one of R^{92} and R^{96} is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy and the other of R^{92} and R^{96} is selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; in further embodiments, one of R^{92} and R^{96} is selected from hydrogen, fluoro or chloro and the other of R^{92} and R^{96} is selected from fluoro or chloro; in further embodiments, R^{92} is fluoro and R^{96} is selected from hydrogen, fluoro, or chloro; in further embodiments, R^{92} and R^{96} are both fluoro.

[0067] In some embodiments, compounds of Formula VII have the structure according to the following sub-generic structure Formula VIIb:



Formula VIIb

wherein:

X is O or S;

R^{84} is selected from the group consisting of hydrogen, lower alkoxy, $-OH$, and $-Cl$;

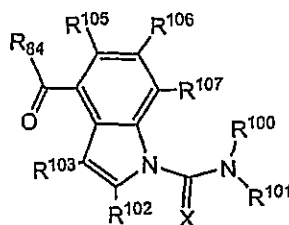
R^{92} , R^{94} , R^{95} , and R^{96} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy;

R^{82} is hydrogen or lower alkyl;

one of R^{100} and R^{101} is lower alkyl, fluoro substituted lower alkyl, or $-(CH_2)_{0-2}R^{70}$, and the other of R^{100} and R^{101} is hydrogen or lower alkyl; or R^{100} and R^{101} together with the nitrogen to which they are attached form optionally substituted 5-7 membered heterocycloalkyl or optionally substituted 5 or 7 membered nitrogen containing heteroaryl; and R^{70} is selected from the group consisting of optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl.

[0068] In some embodiments of compounds of Formula VIIb, at least two of R^{92} , R^{94} , R^{95} and R^{96} are hydrogen. In some embodiments, at least two of R^{92} , R^{94} , R^{95} and R^{96} are hydrogen, and R^{70} is aryl or heteroaryl, wherein aryl and 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.

[0069] In some embodiments, compounds of Formula VIII have the structure according to the following sub-generic structure Formula VIIIa:



Formula VIIIa

wherein:

X is O or S;

R^{84} is selected from the group consisting of hydrogen, lower alkoxy, -OH, and -Cl;

R^{102} , R^{103} , R^{105} , R^{106} , and R^{107} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy;

one of R^{100} and R^{101} is lower alkyl, fluoro substituted lower alkyl, or $-(CH_2)_{0-2}R^{70}$ and the other of R^{100} and R^{101} is hydrogen or lower alkyl;

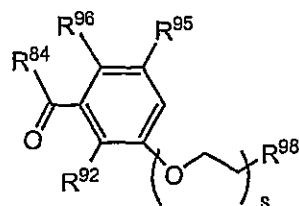
or R^{100} and R^{101} together with the nitrogen to which they are attached form optionally substituted 5-7 membered heterocycloalkyl or optionally substituted 5 or 7 membered nitrogen containing heteroaryl; and

R^{70} is selected from the group consisting of optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl.

[0070] In some embodiments of compounds of Formula VIIIa, at least two, also at least three, also at least four, or all of R^{102} , R^{103} , R^{105} , R^{106} , and R^{107} are hydrogen. In some embodiments, at least two,

also at least three, also at least four, or all of R^{102} , R^{103} , R^{105} , R^{106} , and R^{107} are hydrogen, and R^{70} is aryl or heteroaryl, wherein aryl and 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.

[0071] In some embodiments, compounds of Formula IX have the structure according to the following sub-generic structure Formula IXa:



Formula IXa

wherein:

R^{84} is selected from the group consisting of hydrogen, lower alkoxy, -OH, and -Cl;

R^{92} , R^{95} , and R^{96} are independently selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy;

R^{98} is selected from the group consisting of hydrogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy; and

s is 0, 1, or 2.

[0072] In some embodiments of any of the above embodiments of compounds of Formula IVa, IVb, Va, VIa, VIb, VIIa, VIIb, VIIIa, or IXa, R^{84} is hydrogen.

[0073] In some 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; 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 some embodiments compounds which include linkages such as the following are excluded from the present invention: -NR-CH₂-NR-, -O-CH₂-NR-, -S-CH₂-NR-, -NR-CH₂-O-, -O-CH₂-O-, -S-CH₂-O-, -NR-CH₂-S-, -O-CH₂-S-, -S-CH₂-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-.

[0074] 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 III, it is understood that such reference includes compounds of Formulae IIIa-IIIq, and all sub-embodiments thereof.

[0075] In one aspect, the invention provides methods for treating a protein kinase mediated disease or condition in an animal subject, wherein the method involves administering to the subject an effective amount of a compound of Formula III. The terms "treat," "therapy," and like terms refer to the administration of material, e.g., compound of Formula III, in an amount effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or condition, i.e., indication, and/or to prolong the survival of the subject being treated. The term "protein kinase mediated disease or condition" refers to a disease or condition in which the biological function of a protein kinase affects the development and/or course of the disease or condition, and/or in which modulation of the protein kinase alters the development, course, and/or symptoms of the disease or condition. A protein kinase mediated disease or condition includes a disease or condition for which modulation provides a therapeutic benefit, e.g. wherein treatment with protein kinase inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition. In one aspect, the method involves administering to the subject an effective amount of a compound of Formula III in combination with one or more other therapies for the disease or condition.

[0076] In one aspect, the invention provides methods for treating a Raf protein kinase mediated disease or condition in an animal subject, wherein the method involves administering to the subject an effective amount of a compound of Formula III. The terms "Raf protein kinase mediated disease or condition," "Raf mediated disease or condition," and the like refer to a disease or condition in which the biological function of a Raf kinase, including any mutations thereof, affects the development and/or course of the disease or condition, and/or in which modulation of the Raf protein kinase alters the development, course, and/or symptoms of the disease or condition. The Raf protein kinase includes, but is not limited to, B-Raf, mutations of B-Raf, c-Raf-1 and mutations of c-Raf-1. In some embodiments, the Raf protein kinase is B-Raf mutation V600E. In further embodiments, the disease or condition is a cancer that is amenable to treatment by an inhibitor of the V600E mutant B-Raf. A Raf protein kinase mediated disease or condition includes a disease or condition for which Raf inhibition provides a therapeutic benefit, e.g. wherein treatment with Raf inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition. In one aspect, the method involves administering to the subject an effective amount of a compound of Formula III in combination with one or more other therapies for the disease or condition.

[0077] In one aspect, the invention provides methods for treating a Fms protein kinase mediated disease or condition in an animal subject, wherein the method involves administering to the subject an

effective amount of a compound of Formula III. The terms "Fms protein kinase mediated disease or condition," "Fms mediated disease or condition," and the like refer to a disease or condition in which the biological function of a Fms protein kinase, including any mutations thereof, affects the development and/or course of the disease or condition, and/or in which modulation of Fms alters the development, course, and/or symptoms of the disease or condition. A Fms mediated disease or condition includes a disease or condition for which Fms inhibition provides a therapeutic benefit, e.g. wherein treatment with Fms inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition. In one aspect, the method involves administering to the subject an effective amount of a compound of Formula III in combination with one or more other therapies for the disease or condition.

[0078] In one aspect, the invention provides methods for treating a Kit protein kinase mediated disease or condition in an animal subject, wherein the method involves administering to the subject an effective amount of a compound of Formula III. The terms "Kit mediated disease or condition," "Kit protein kinase mediated disease or condition," and the like refer to a disease or condition in which the biological function of a Kit protein kinase, including any mutation thereof, affects the development and/or course of the disease or condition, and/or in which modulation of Kit alters the development, course, and/or symptoms of the disease or condition. A Kit mediated disease or condition includes a disease or condition for which Kit inhibition provides a therapeutic benefit, e.g. wherein treatment with Kit inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition. In one aspect, the method involves administering to the subject an effective amount of a compound of Formula III in combination with one or more other therapies for the disease or condition.

[0079] In one aspect, the invention provides methods for treating a Jnk protein kinase mediated disease or condition in an animal subject, wherein the method involves administering to the subject an effective amount of a compound of Formula III. The terms "Jnk mediated disease or condition," "Jnk protein kinase mediated disease or condition," and the like refer to a disease or condition in which the biological function of a Jnk kinase, e.g. Jnk1, Jnk2, Jnk3, or any mutation thereof, affects the development and/or course of the disease or condition, and/or in which modulation of the Jnk kinase alters the development, course, and/or symptoms of the disease or condition. A Jnk mediated disease or condition includes a disease or condition for which Jnk inhibition provides a therapeutic benefit, e.g. wherein treatment with Jnk inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition. In one aspect, the method involves administering to the subject an effective amount of a compound of Formula III in combination with one or more other therapies for the disease or condition. The Jnk protein kinase includes, but is not limited to, Jnk1, Jnk2, or Jnk3.

[0080] In some embodiments, a compound of the invention has an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted kinase activity assay. In some embodiments, a compound of Formula III will have an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM with respect to at least one kinase selected from the group consisting of B-Raf, c-Raf-1, Fms, Jnk1, Jnk2, Jnk3, and Kit, and any mutations thereof. In some embodiments, a compound of Formula III will have an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM with respect to at least one kinase selected from the group consisting of B-Raf, B-Raf V600E mutant, c-Raf-1, Fms, Jnk1, Jnk2, Jnk3, and Kit, preferably B-Raf, B-Raf V600E mutant or c-Raf-1.

[0081] In some embodiments, a compound of Formula III is an inhibitor of a Raf kinase and has an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted Raf kinase activity assay. In some embodiments, a compound of Formula III will have an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM with respect to B-Raf, c-Raf-1, or B-Raf V600E mutant. In some embodiments, a compound of Formula III will selectively inhibit one Raf kinase relative to one or more other Raf kinases. In some embodiments, the compound of Formula III will selectively inhibit a mutation of the Raf kinase relative to the wild type kinase, for example B-Raf V600E relative to wild type B-Raf.

[0082] In some embodiments, a compound of Formula III is an inhibitor of a Fms kinase and has an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted Fms kinase activity assay. In some embodiments, a compound of Formula III will selectively inhibit Fms kinase relative to Kit kinase.

[0083] In some embodiments, a compound of Formula III is an inhibitor of a Kit kinase and has an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted Kit kinase activity assay.

[0084] In some embodiments, a compound of Formula III is an inhibitor of a Jnk kinase and has an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted Jnk kinase activity assay. In some embodiments, a compound of Formula III is an inhibitor of a Jnk1 kinase and has an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted Jnk1 kinase activity assay. In some embodiments, a compound of Formula III is an inhibitor of a Jnk2 kinase and has an IC_{50} of less than 500 nM, less

than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted Jnk2 kinase activity assay. In some embodiments, a compound of Formula III is an inhibitor of a Jnk3 kinase and has an IC_{50} of less than 500 nM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted Jnk3 kinase activity assay. In some embodiments, a compound of Formula III will selectively inhibit one Jnk kinase relative to one or more other Jnk kinases, such as selectively inhibiting Jnk 1 relative to Jnk 2 and/or Jnk3, selectively inhibiting Jnk2 relative to Jnk3 and/or Jnk1, or selectively inhibiting Jnk3 relative to Jnk1 and/or Jnk 2.

[0085] Further to any of the above mentioned embodiments, a compound of the invention will inhibit the effects of a mutation of the kinase, including, but not limited to, a mutation that is related to a disease state, such as a cancer. For example, B-Raf V600E mutant is present in a high percentage of some cancers, such as melanoma, and compounds of the invention will inhibit the kinase activity of this mutant.

[0086] Further to any of the above embodiments, a compound of the invention may selectively inhibit one kinase relative to one or more other kinases, where preferably inhibition is selective with respect to any of the other kinases, whether a kinase discussed herein, or other kinases. In some embodiments, the compound may selectively inhibit the effects of a mutation of the kinase relative to the wild type kinase, for example B-Raf V600E relative to wild type B-Raf. In some embodiments, the compound may selectively inhibit Fms relative to Kit. Selective inhibition of one kinase relative to another is such that the IC_{50} for the one kinase may be at least about 2-fold, also 5-fold, also 10-fold, also 20-fold, also 50-fold, or at least about 100-fold less than the IC_{50} for any of the other kinases as determined in a generally accepted kinase activity assay.

[0087] In another aspect, the invention provides methods for treating a protein kinase mediated disease or condition in an animal subject, wherein the method involves administering to the subject an effective amount of a composition including a compound of Formula III.

[0088] In one aspect, the invention provides methods for treating a disease or condition mediated by a protein kinase selected from the group consisting of B-Raf, c-Raf-1, Fms, Jnk1, Jnk2, Jnk3, and Kit, and any mutations thereof, by administering to the subject an effective amount of a composition including a compound of Formula III.

[0089] In one aspect, the invention provides methods for treating a disease or condition mediated by B-Raf, c-Raf-1, or B-Raf V600E by administering to the subject an effective amount of a composition including a compound of Formula III. In one aspect, the invention provides methods for treating a disease or condition mediated by B-Raf, c-Raf-1, or B-Raf V600E by administering to the

subject an effective amount of a composition including a compound of Formula III in combination with one or more other suitable therapies for treating the disease or condition. In one aspect, the invention provides methods for treating a cancer mediated by B-Raf V600E mutant by administering to the subject an effective amount of a composition including a compound of Formula III in combination with one or more suitable anticancer therapies, such as one or more chemotherapeutic drugs.

[0090] 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 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. 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 III, a prodrug of such compound, or a pharmaceutically acceptable salt of such compound or prodrug in combination with one or more other suitable therapies for the disease or condition.

[0091] In another aspect, the invention provides compositions that include a therapeutically effective amount of a compound of Formula III and at least one pharmaceutically acceptable carrier, excipient, and/or diluent. The composition can include a plurality of different pharmacologically active compounds, which can include a plurality of compounds of Formula III.

[0092] In a related aspect, the invention provides kits that include a composition as described herein. In some 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 protein kinase mediated disease or condition; the invention kit includes written instructions for use and/or other indication that the composition is suitable or approved for administration to a mammal, e.g., a human, for a protein kinase-mediated disease or condition; and the composition is packaged in unit dose or single dose form, e.g., single dose pills, capsules, or the like.

[0093] In aspects involving treatment or prophylaxis of a disease or condition with the compounds of Formula III, the disease or condition is, for example without limitation, selected from the group consisting of neurologic diseases such as ischemic stroke, cerebrovascular ischemia, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease, amyotrophic lateral sclerosis, dementia, senile chorea, and Huntington's disease; neoplastic diseases and associated complications, including chemotherapy-induced hypoxia, gastrointestinal stromal tumors (GISTs), prostate tumors, mast cell tumors (including canine mast cell tumors), acute myeloid leukemia, acute

lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, melanoma, mastocytosis, gliomas, glioblastoma, astrocytoma, neuroblastoma, sarcomas (e.g. sarcomas of neuroectodermal origin), carcinomas (e.g. lung, breast, pancreatic, renal, female genital tract, carcinoma in situ), lymphoma (e.g. histiocytic lymphoma), neurofibromatosis (including Schwann cell neoplasia), myelodysplastic syndrome, leukemia, tumor angiogenesis, and cancers of the thyroid, liver, bone, skin, brain, pancreas, lung (e.g. small cell lung cancer), breast, colon, prostate, testes and ovary; pain of neuropathic or inflammatory origin, including acute pain, chronic pain, and migraine; cardiovascular diseases including heart failure, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, reperfusion injury and ischemia (e.g. cerebrovascular ischemia, liver ischemia); inflammation including, but not limited to, polycystic kidney disease (PKD), age-related macular degeneration, rheumatoid arthritis, allergic rhinitis, inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, systemic lupus erythematosus, Sjogren's Syndrome, Wegener's granulomatosis, psoriasis, scleroderma, chronic thyroiditis, Grave's disease, myasthenia gravis, multiple sclerosis, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, hyper eosinophilia, CNS inflammation, pancreatitis, nephritis, atopic dermatitis, and hepatitis; immunodeficiency diseases, organ transplant rejection, graft versus host disease; renal or prostatic diseases including diabetic nephropathy, nephrosclerosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, prostate hyperplasia, chronic renal failure, tubular necrosis, diabetes-associated renal complications, and hypertrophy; metabolic diseases including type 1 diabetes, type 2 diabetes, metabolic syndrome, obesity, hepatic steatosis, insulin resistance, hyperglycemia, lipolysis and obesity; infection, including, but not limited to *Helicobacter pylori* and *Influenza virus*, fever, sepsis; pulmonary diseases including chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), asthma, allergy, bronchitis, emphysema, and pulmonary fibrosis; genetic developmental diseases such as Noonan's syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), leopard syndrome, cardio-faciocutaneous syndrome (CFC) and neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases; and disorders of bone structure or mineralization, including osteoporosis, increased risk of fracture, hypercalcemia, and bone metastases.

[0094] In a related aspect, compounds of Formula III, can be used in the preparation of a medicament for the treatment of a B-Raf-mediated disease or condition, selected from the group consisting of neurologic diseases such as ischemic stroke, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease; neoplastic diseases including, but not limited to, melanoma, glioma, sarcoma, carcinoma (e.g. lung, breast, pancreatic, renal), lymphoma (e.g. histiocytic lymphoma) and cancer of the thyroid, lung (e.g. small cell lung cancer), liver, breast, ovary and colon, neurofibromatosis, myelodysplastic syndrome, leukemia, tumor angiogenesis; pain of neuropathic or inflammatory origin, including acute pain, chronic pain, and migraine;

cardiovascular diseases including heart failure, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, reperfusion injury; inflammation including, but not limited to, psoriasis, polycystic kidney disease (PKD), arthritis and autoimmune diseases and conditions, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease (IBD); immunodeficiency diseases, organ transplant rejection, graft versus host disease; renal or prostatic diseases including diabetic nephropathy, nephrosclerosis, glomerulonephritis, prostate hyperplasia; metabolic disorders, obesity; infection, including, but not limited to *Helicobacter pylori* and *Influenza virus*, fever, sepsis; pulmonary diseases including chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS); genetic developmental diseases such as Noonan's syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), leopard syndrome, cardio-faciocutaneous syndrome (CFC), and neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases.

[0095] In a related aspect, compounds of Formula III, can be used in the preparation of a medicament for the treatment of a c-Raf-1-mediated disease or condition selected from the group consisting of colorectal, ovarian, lung and renal cell carcinoma, acute myeloid leukemia, myelodysplastic syndromes, tumor angiogenesis, and neuroendocrine tumors such as medullary thyroid cancer, carcinoid, small cell lung cancer and pheochromocytoma.

[0096] In a related aspect, compounds of Formula III, can be used in the preparation of a medicament for the treatment of a Fms-mediated disease or condition selected from the group consisting of immune disorders, including rheumatoid arthritis, systemic lupus erythematosus (SLE), Wegener's granulomatosis, and transplant rejection, inflammatory diseases including Chronic Obstructive Pulmonary Disease (COPD), emphysema, and atherosclerosis, metabolic disorders, including insulin resistance, hyperglycemia, and lipolysis, disorders of bone structure or mineralization, including osteoporosis, increased risk of fracture, hypercalcemia, and bone metastases, kidney diseases, including nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications, and hypertrophy and cancers, including multiple myeloma, acute myeloid leukemia, chronic myeloid leukemia (CML), breast cancer, and ovarian cancer.

[0097] In a related aspect, compounds of Formula III, can be used in the preparation of a medicament for the treatment of a Jnk-mediated disease or condition selected from the group consisting of Metabolic diseases including type 1 diabetes, type 2 diabetes, metabolic syndrome, obesity, and hepatic steatosis; cardiovascular diseases such as atherosclerosis, ischemia (e.g. cerebrovascular ischemia, liver ischemia), reperfusion injury, cardiac hypertrophy; renal diseases such as chronic renal failure; neoplastic diseases and associated complications, including chemotherapy-induced hypoxia, prostate tumors, myeloid leukemia and cancers of the liver, bone, skin, brain,

pancreas, lung breast, colon, prostate and ovary; transplant rejection; pain of neuropathic or inflammatory origin including acute and chronic pain; inflammatory and autoimmune diseases including age-related macular degeneration, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, Sjogren's Syndrome, psoriasis, scleroderma, chronic thyroiditis, Grave's disease, myasthenia gravis, and multiple sclerosis, and inflammation in other organs including CNS inflammation, pancreatitis, nephritis, atopic dermatitis, and hepatitis; airway inflammatory diseases such as asthma, allergy, bronchitis, pulmonary fibrosis, chronic obstructive pulmonary disease; neurologic diseases such as stroke, cerebrovascular ischemia, neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, dementia, senile chorea, head and spinal cord trauma, and Huntington's disease.

[0098] In a related aspect, compounds of Formula III, can be used in the preparation of a medicament for the treatment of a Jnk1-mediated disease or condition selected from the group consisting of type 1 diabetes, type 2 diabetes, metabolic syndrome, obesity and hepatic steatosis.

[0099] In a related aspect, compounds of Formula III, can be used in the preparation of a medicament for the treatment of a Jnk2-mediated disease or condition, such as atherosclerosis.

[0100] In a related aspect, compounds of Formula III, can be used in the preparation of a medicament for the treatment of a Jnk3-mediated disease or condition selected from the group consisting of inflammatory diseases including autoimmune diseases such as rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosus, Sjogren's Syndrome, psoriasis and multiple sclerosis, airway inflammatory diseases such as asthma, allergy, pulmonary fibrosis, and chronic obstructive pulmonary disease, and inflammation in other organs, such as CNS inflammation, pancreatitis, nephritis, and hepatitis; neurologic diseases such as stroke, cerebrovascular ischemia, and neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Huntington's disease; and neoplastic diseases such as prostate tumors and myeloid leukemia.

[0101] In a related aspect, compounds of Formula III, can be used in the preparation of a medicament for the treatment of a Kit-mediated disease or condition selected from the group consisting of 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.

[0102] Additional aspects and embodiments will be apparent from the following Detailed Description and from the claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As used herein the following definitions apply unless clearly indicated otherwise:

[0103] "Halogen" refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0104] "Hydroxyl" or "hydroxy" refer to the group -OH.

[0105] "Thiol" refers to the group -SH.

[0106] "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. A "substituted lower alkyl" denotes lower alkyl that is independently substituted, unless indicated otherwise, 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, wherein the substituents are selected from the group consisting of -F, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^o, -SR^o, -OC(O)R^o, -OC(S)R^o, -C(O)R^o, -C(S)R^o, -C(O)OR^o, -C(S)OR^o, -S(O)R^o, -S(O)₂R^o, -C(O)NHR^o, -C(S)NHR^o, -C(O)NR^oR^o, -C(S)NR^oR^o, -S(O)₂NHR^o, -S(O)₂NR^oR^o, -C(NH)NHR^o, -C(NH)NR^oR^o, -NHC(O)R^o, -NHC(S)R^o, -NR^oC(O)R^o, -NR^oC(S)R^o, -NHS(O)₂R^o, -NR^oS(O)₂R^o, -NHC(O)NHR^o, -NHC(S)NHR^o, -NR^oC(O)NH₂, -NR^oC(S)NH₂, -NR^oC(O)NHR^o, -NR^oC(S)NHR^o, -NHC(O)NR^oR^o, -NHC(S)NR^oR^o, -NR^oC(O)NR^oR^o, -NR^oC(S)NR^oR^o, -NHS(O)₂NHR^o, -NR^oS(O)₂NH₂, -NR^oS(O)₂NHR^o, -NHS(O)₂NR^oR^o, -NR^oS(O)₂NR^oR^o, -NHR^o, -NR^oR^o, -R^e, -R^f, and -R^g. Furthermore, possible substitutions include subsets of these substitutions, such as are indicated herein, for example, in the description of compounds of Formula III, 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 (e.g. alkoxy), -SR (e.g. thioalkyl), -NHR (e.g. alkylamino), -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. "C₂₋₆ alkyl" denotes lower alkyl containing 2-6 carbon atoms. A "substituted C₂₋₆ alkyl" denotes optionally substituted lower alkyl containing 2-6 carbon atoms. A "substituted methyl" denotes methyl that is independently substituted, unless indicated otherwise, with 1, 2, or 3 substituents, wherein the substituents are selected as per optionally substituted lower alkyl.

[0107] "C₁₋₃ alkylene" refers to a divalent alkane-derived radical containing 1-3 carbon atoms, straight chain or branched, from which two hydrogen atoms are taken from the same carbon atom or from different carbon atoms. C₁₋₃ alkylene includes methylene -CH₂-, ethylene -CH₂CH₂-, propylene -CH₂CH₂CH₂-, and isopropylene -CH(CH₃)CH₂- or -CH₂CH(CH₃)-. C₁₋₃ alkylene substituted with one or more substituents indicates C₁₋₃ alkylene that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents as indicated, attached at any available atom to produce a stable compound.

[0108] "Lower alkenyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) and at least one, preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. Carbon to carbon double bonds may be either contained within a straight chain or branched portion. Examples of lower alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and the like. A "substituted lower alkenyl" denotes lower alkenyl that is independently substituted, unless indicated otherwise, 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, wherein the substituents are selected from the group consisting of -F, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^o, -SR^o, -OC(O)R^o, -OC(S)R^o, -C(O)R^o, -C(S)R^o, -C(O)OR^o, -C(S)OR^o, -S(O)R^o, -S(O)₂R^o, -C(O)NHR^o, -C(S)NHR^o, -C(O)NR^oR^o, -C(S)NR^oR^o, -S(O)₂NHR^o, -S(O)₂NR^oR^o, -C(NH)NHR^o, -C(NH)NR^oR^o, -NHC(O)R^o, -NHC(S)R^o, -NR^oC(O)R^o, -NR^oC(S)R^o, -NHS(O)₂R^o, -NR^oS(O)₂R^o, -NHC(O)NHR^o, -NHC(S)NHR^o, -NR^oC(O)NH₂, -NR^oC(S)NH₂, -NR^oC(O)NHR^o, -NR^oC(S)NHR^o, -NHC(O)NR^oR^o, -NHC(S)NR^oR^o, -NR^oC(O)NR^oR^o, -NR^oC(S)NR^oR^o, -NHS(O)₂NHR^o, -NR^oS(O)₂NH₂, -NR^oS(O)₂NHR^o, -NHS(O)₂NR^oR^o, -NR^oS(O)₂NR^oR^o, -NHR^o, -NR^oR^o, -R^d, -R^f, and -R^g. Further, possible substitutions include subsets of these substitutions, such as are indicated herein, for example, in the description of compounds of Formula III, attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkenyl" denotes a lower alkenyl group substituted with one or more fluoro atoms, where preferably the lower alkenyl 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, substitution of alkenyl groups are such that -F, -C(O)-, -C(S)-, -C(NH)-, -S(O)-,

-S(O)₂-, -O-, -S-, or N (except where N is a heteroaryl ring atom), are not bound to an alkene carbon thereof. Further, where alkenyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)R, and the like, substitution of the moiety is such that any -C(O)-, -C(S)-, -S(O)-, -S(O)₂-, -O-, -S-, or N thereof (except where N is a heteroaryl ring atom) are not bound to an alkene carbon of the alkenyl substituent or R group. Further, where alkenyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the alkenyl R group is such that substitution of the alkenyl 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 alkenyl carbon bound to any O, S, or N of the moiety. An "alkenyl carbon" refers to any carbon within an alkenyl group, whether saturated or part of the carbon to carbon double bond. An "alkene carbon" refers to a carbon within an alkenyl group that is part of a carbon to carbon double bond.

[0109] "Lower alkynyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl, and the like. A "substituted lower alkynyl" denotes lower alkynyl that is independently substituted, unless indicated otherwise, 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, wherein the substituents are selected from the group consisting of -F, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^o, -SR^o, -OC(O)R^o, -OC(S)R^o, -C(O)R^o, -C(S)R^o, -C(O)OR^o, -C(S)OR^o, -S(O)R^o, -S(O)₂R^o, -C(O)NHR^o, -C(S)NHR^o, -C(O)NR^oR^o, -C(S)NR^oR^o, -S(O)₂NHR^o, -S(O)₂NR^oR^o, -C(NH)NHR^o, -C(NH)NR^oR^o, -NHC(O)R^o, -NHC(S)R^o, -NR^oC(O)R^o, -NR^oC(S)R^o, -NHS(O)₂R^o, -NR^oS(O)₂R^o, -NHC(O)NHR^o, -NHC(S)NHR^o, -NR^oC(O)NH₂, -NR^oC(S)NH₂, -NR^oC(O)NHR^o, -NR^oC(S)NHR^o, -NHC(O)NR^oR^o, -NHC(S)NR^oR^o, -NR^oC(O)NR^oR^o, -NR^oC(S)NR^oR^o, -NHS(O)₂NHR^o, -NR^oS(O)₂NH₂, -NR^oS(O)₂NHR^o, -NHS(O)₂NR^oR^o, -NR^oS(O)₂NR^oR^o, -NHR^o, -NR^oR^o, -R^d, -R^e, and -R^f. Further, possible substitutions include subsets of these substitutions, such as are indicated herein, for example, in the description of compounds of Formula III, attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkynyl" denotes a lower alkynyl group substituted with one or more fluoro atoms, where preferably the lower alkynyl 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, substitution of alkynyl groups are such that -F, -C(O)-, -C(S)-, -C(NH)-, -S(O)-, -S(O)₂-, -O-, -S-, or N (except where N is a heteroaryl ring atom) are not bound to an alkyne carbon thereof. Further, where alkynyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)R, and the like, substitution of the moiety is such that any -C(O)-, -C(S)-, -S(O)-, -S(O)₂-, -O-, -S-, or N thereof (except where N is a heteroaryl ring atom) are not bound

to an alkyne carbon of the alkynyl substituent or R group. Further, where alkynyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the alkynyl R group is such that substitution of the alkynyl 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 alkynyl carbon bound to any O, S, or N of the moiety. An "alkynyl carbon" refers to any carbon within an alkynyl group, whether saturated or part of the carbon to carbon triple bond. An "alkyne carbon" refers to a carbon within an alkynyl group that is part of a carbon to carbon triple bond.

[0110] "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, unless indicated otherwise, 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, wherein the substituents are selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^o, -SR^o, -OC(O)R^o, -OC(S)R^o, -C(O)R^o, -C(S)R^o, -C(O)OR^o, -C(S)OR^o, -S(O)R^o, -S(O)₂R^o, -C(O)NHR^o, -C(S)NHR^o, -C(O)NR^oR^o, -C(S)NR^oR^o, -S(O)₂NHR^o, -S(O)₂NR^oR^o, -C(NH)NHR^o, -C(NH)NR^oR^o, -NHC(O)R^o, -NHC(S)R^o, -NR^oC(O)R^o, -NR^oC(S)R^o, -NHS(O)₂R^o, -NR^oS(O)₂R^o, -NHC(O)NHR^o, -NHC(S)NHR^o, -NR^oC(O)NH₂, -NR^oC(S)NH₂, -NR^oC(O)NHR^o, -NR^oC(S)NHR^o, -NHC(O)NR^oR^o, -NHC(S)NR^oR^o, -NR^oC(O)NR^oR^o, -NR^oC(S)NR^oR^o, -NHS(O)₂NHR^o, -NR^oS(O)₂NH₂, -NR^oS(O)₂NHR^o, -NHS(O)₂NR^oR^o, -NR^oS(O)₂NR^oR^o, -NHR^o, -NR^oR^o, -R^d, -R^e, -R^f, and -R^g.

[0111] "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 a ring carbon may be 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, unless indicated otherwise, 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, wherein the substituents are selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH,

-C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂,
 -C(NH)NH₂, -OR^o, -SR^o, -OC(O)R^o, -OC(S)R^o, -C(O)R^o, -C(S)R^o, -C(O)OR^o, -C(S)OR^o, -S(O)R^o,
 -S(O)₂R^o, -C(O)NHR^o, -C(S)NHR^o, -C(O)NR^oR^o, -C(S)NR^oR^o, -S(O)₂NHR^o, -S(O)₂NR^oR^o,
 -C(NH)NHR^o, -C(NH)NR^oR^o, -NHC(O)R^o, -NHC(S)R^o, -NR^oC(O)R^o, -NR^oC(S)R^o, -NHS(O)₂R^o,
 -NR^oS(O)₂R^o, -NHC(O)NHR^o, -NHC(S)NHR^o, -NR^oC(O)NH₂, -NR^oC(S)NH₂, -NR^oC(O)NHR^o,
 -NR^oC(S)NHR^o, -NHC(O)NR^oR^o, -NHC(S)NR^oR^o, -NR^oC(O)NR^oR^o, -NR^oC(S)NR^oR^o,
 -NHS(O)₂NHR^o, -NR^oS(O)₂NH₂, -NR^oS(O)₂NHR^o, -NHS(O)₂NR^oR^o, -NR^oS(O)₂NR^oR^o, -NHR^o,
 -NR^oR^o, -R^d, -R^e, -R^f, and -R^g.

[0112] "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, unless indicated otherwise, 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, wherein the substituents are selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^o, -SR^o, -OC(O)R^o, -OC(S)R^o, -C(O)R^o, -C(S)R^o, -C(O)OR^o, -C(S)OR^o, -S(O)R^o, -S(O)₂R^o, -C(O)NHR^o, -C(S)NHR^o, -C(O)NR^oR^o, -C(S)NR^oR^o, -S(O)₂NHR^o, -S(O)₂NR^oR^o, -C(NH)NHR^o, -C(NH)NR^oR^o, -NHC(O)R^o, -NHC(S)R^o, -NR^oC(O)R^o, -NR^oC(S)R^o, -NHS(O)₂R^o, -NR^oS(O)₂R^o, -NHC(O)NHR^o, -NHC(S)NHR^o, -NR^oC(O)NH₂, -NR^oC(S)NH₂, -NR^oC(O)NHR^o, -NR^oC(S)NHR^o, -NHC(O)NR^oR^o, -NHC(S)NR^oR^o, -NR^oC(O)NR^oR^o, -NR^oC(S)NR^oR^o, -NHS(O)₂NHR^o, -NR^oS(O)₂NH₂, -NR^oS(O)₂NHR^o, -NHS(O)₂NR^oR^o, -NR^oS(O)₂NR^oR^o, -NHR^o, -NR^oR^o, -R^d, -R^e, -R^f, and -R^g.

[0113] "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, quinoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinoliny, pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, 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, unless indicated otherwise, 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, wherein the

substituents are selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^o, -SR^o, -OC(O)R^o, -OC(S)R^o, -C(O)R^o, -C(S)R^o, -C(O)OR^o, -C(S)OR^o, -S(O)R^o, -S(O)₂R^o, -C(O)NHR^o, -C(S)NHR^o, -C(O)NR^oR^o, -C(S)NR^oR^o, -S(O)₂NHR^o, -S(O)₂NR^oR^o, -C(NH)NHR^o, -C(NH)NR^oR^o, -NHC(O)R^o, -NHC(S)R^o, -NR^oC(O)R^o, -NR^oC(S)R^o, -NHS(O)₂R^o, -NR^oS(O)₂R^o, -NHC(O)NHR^o, -NHC(S)NHR^o, -NR^oC(O)NH₂, -NR^oC(S)NH₂, -NR^oC(O)NHR^o, -NR^oC(S)NHR^o, -NHC(O)NR^oR^o, -NHC(S)NR^oR^o, -NR^oC(O)NR^oR^o, -NR^oC(S)NR^oR^o, -NHS(O)₂NHR^o, -NR^oS(O)₂NH₂, -NR^oS(O)₂NHR^o, -NHS(O)₂NR^oR^o, -NR^oS(O)₂NR^oR^o, -NHR^o, -NR^oR^o, -R^d, -R^e, -R^f, and -R^g.

[0114] The variables R^o, R^p, R^c, R^d, R^e, R^f and R^g as used in the description of optional substituents for alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are defined as follows:

each R^o, R^p, and R^c are independently selected from the group consisting of R^d, R^e, R^f, and R^g, or R^p and R^c combine with the nitrogen to which they are attached to form a 5-7 membered heterocycloalkyl or a 5 or 7 membered nitrogen containing heteroaryl, wherein the 5-7 membered heterocycloalkyl or 5 or 7 membered nitrogen containing heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, -NO₂, -CN, -OH, -NH₂, -OR^u, -SR^u, -NHR^u, -NR^uR^u, -R^x, and -R^y;

each R^d is independently lower alkyl, wherein lower alkyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of fluoro, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^k, -SR^k, -OC(O)R^k, -OC(S)R^k, -C(O)R^k, -C(S)R^k, -C(O)OR^k, -C(S)OR^k, -S(O)R^k, -S(O)₂R^k, -C(O)NHR^k, -C(S)NHR^k, -C(O)NR^kR^k, -C(S)NR^kR^k, -S(O)₂NHR^k, -S(O)₂NR^kR^k, -C(NH)NHR^k, -C(NH)NR^mRⁿ, -NHC(O)R^k, -NHC(S)R^k, -NR^kC(O)R^k, -NR^kC(S)R^k, -NHS(O)₂R^k, -NR^kS(O)₂R^k, -NHC(O)NHR^k, -NHC(S)NHR^k, -NR^kC(O)NH₂, -NR^kC(S)NH₂, -NR^kC(O)NHR^k, -NR^kC(S)NHR^k, -NHC(O)NR^kR^k, -NHC(S)NR^kR^k, -NR^kC(O)NR^kR^k, -NR^kC(S)NR^kR^k, -NHS(O)₂NHR^k, -NR^kS(O)₂NH₂, -NR^kS(O)₂NHR^k, -NHS(O)₂NR^kR^k, -NR^kS(O)₂NR^kR^k, -NHR^k, -NR^kR^k, -Rⁱ, and -R^j;

each R^e is independently lower alkenyl, wherein lower alkenyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of fluoro, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^k, -SR^k, -OC(O)R^k, -OC(S)R^k, -C(O)R^k, -C(S)R^k, -C(O)OR^k, -C(S)OR^k, -S(O)R^k, -S(O)₂R^k, -C(O)NHR^k, -C(S)NHR^k, -C(O)NR^kR^k, -C(S)NR^kR^k, -S(O)₂NHR^k, -S(O)₂NR^kR^k, -C(NH)NHR^k, -C(NH)NR^mRⁿ, -NHC(O)R^k, -NHC(S)R^k, -NR^kC(O)R^k, -NR^kC(S)R^k, -NHS(O)₂R^k, -NR^kS(O)₂R^k, -NHC(O)NHR^k, -NHC(S)NHR^k, -NR^kC(O)NH₂,

$-\text{NR}^k\text{C}(\text{S})\text{NH}_2$, $-\text{NR}^k\text{C}(\text{O})\text{NHR}^k$, $-\text{NR}^k\text{C}(\text{S})\text{NHR}^k$, $-\text{NHC}(\text{O})\text{NR}^k\text{R}^k$, $-\text{NHC}(\text{S})\text{NR}^k\text{R}^k$, $-\text{NR}^k\text{C}(\text{O})\text{NR}^k\text{R}^k$,
 $-\text{NR}^k\text{C}(\text{S})\text{NR}^k\text{R}^k$, $-\text{NHS}(\text{O})_2\text{NHR}^k$, $-\text{NR}^k\text{S}(\text{O})_2\text{NH}_2$, $-\text{NR}^k\text{S}(\text{O})_2\text{NHR}^k$, $-\text{NHS}(\text{O})_2\text{NR}^k\text{R}^k$,
 $-\text{NR}^k\text{S}(\text{O})_2\text{NR}^k\text{R}^k$, $-\text{NHR}^k$, $-\text{NR}^k\text{R}^k$, $-\text{R}^h$, and $-\text{R}^j$;

each R^f is independently lower alkynyl, wherein lower alkynyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of fluoro, $-\text{OH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{S})\text{OH}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{S})\text{NH}_2$, $-\text{S}(\text{O})_2\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{S})\text{NH}_2$, $-\text{NHS}(\text{O})_2\text{NH}_2$, $-\text{C}(\text{NH})\text{NH}_2$, $-\text{OR}^k$, $-\text{SR}^k$, $-\text{OC}(\text{O})\text{R}^k$, $-\text{OC}(\text{S})\text{R}^k$, $-\text{C}(\text{O})\text{R}^k$, $-\text{C}(\text{S})\text{R}^k$, $-\text{C}(\text{O})\text{OR}^k$, $-\text{C}(\text{S})\text{OR}^k$, $-\text{S}(\text{O})\text{R}^k$, $-\text{S}(\text{O})_2\text{R}^k$, $-\text{C}(\text{O})\text{NHR}^k$, $-\text{C}(\text{S})\text{NHR}^k$, $-\text{C}(\text{O})\text{NR}^k\text{R}^k$, $-\text{C}(\text{S})\text{NR}^k\text{R}^k$, $-\text{S}(\text{O})_2\text{NHR}^k$, $-\text{S}(\text{O})_2\text{NR}^k\text{R}^k$, $-\text{C}(\text{NH})\text{NHR}^k$, $-\text{C}(\text{NH})\text{NR}^m\text{R}^n$, $-\text{NHC}(\text{O})\text{R}^k$, $-\text{NHC}(\text{S})\text{R}^k$, $-\text{NR}^k\text{C}(\text{O})\text{R}^k$, $-\text{NR}^k\text{C}(\text{S})\text{R}^k$, $-\text{NHS}(\text{O})_2\text{R}^k$, $-\text{NR}^k\text{S}(\text{O})_2\text{R}^k$, $-\text{NHC}(\text{O})\text{NHR}^k$, $-\text{NHC}(\text{S})\text{NHR}^k$, $-\text{NR}^k\text{C}(\text{O})\text{NH}_2$, $-\text{NR}^k\text{C}(\text{S})\text{NH}_2$, $-\text{NR}^k\text{C}(\text{O})\text{NHR}^k$, $-\text{NR}^k\text{C}(\text{S})\text{NHR}^k$, $-\text{NHC}(\text{O})\text{NR}^k\text{R}^k$, $-\text{NHC}(\text{S})\text{NR}^k\text{R}^k$, $-\text{NR}^k\text{C}(\text{O})\text{NR}^k\text{R}^k$, $-\text{NR}^k\text{C}(\text{S})\text{NR}^k\text{R}^k$, $-\text{NHS}(\text{O})_2\text{NHR}^k$, $-\text{NR}^k\text{S}(\text{O})_2\text{NH}_2$, $-\text{NR}^k\text{S}(\text{O})_2\text{NHR}^k$, $-\text{NHS}(\text{O})_2\text{NR}^k\text{R}^k$, $-\text{NR}^k\text{S}(\text{O})_2\text{NR}^k\text{R}^k$, $-\text{NHR}^k$, $-\text{NR}^k\text{R}^k$, $-\text{R}^h$, and $-\text{R}^j$;

each R^g is independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of halogen, $-\text{OH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{S})\text{OH}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{S})\text{NH}_2$, $-\text{S}(\text{O})_2\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{S})\text{NH}_2$, $-\text{NHS}(\text{O})_2\text{NH}_2$, $-\text{C}(\text{NH})\text{NH}_2$, $-\text{OR}^k$, $-\text{SR}^k$, $-\text{OC}(\text{O})\text{R}^k$, $-\text{OC}(\text{S})\text{R}^k$, $-\text{C}(\text{O})\text{R}^k$, $-\text{C}(\text{S})\text{R}^k$, $-\text{C}(\text{O})\text{OR}^k$, $-\text{C}(\text{S})\text{OR}^k$, $-\text{S}(\text{O})\text{R}^k$, $-\text{S}(\text{O})_2\text{R}^k$, $-\text{C}(\text{O})\text{NHR}^k$, $-\text{C}(\text{S})\text{NHR}^k$, $-\text{C}(\text{O})\text{NR}^k\text{R}^k$, $-\text{C}(\text{S})\text{NR}^k\text{R}^k$, $-\text{S}(\text{O})_2\text{NHR}^k$, $-\text{S}(\text{O})_2\text{NR}^k\text{R}^k$, $-\text{C}(\text{NH})\text{NHR}^k$, $-\text{C}(\text{NH})\text{NR}^m\text{R}^n$, $-\text{NHC}(\text{O})\text{R}^k$, $-\text{NHC}(\text{S})\text{R}^k$, $-\text{NR}^k\text{C}(\text{O})\text{R}^k$, $-\text{NR}^k\text{C}(\text{S})\text{R}^k$, $-\text{NHS}(\text{O})_2\text{R}^k$, $-\text{NR}^k\text{S}(\text{O})_2\text{R}^k$, $-\text{NHC}(\text{O})\text{NHR}^k$, $-\text{NHC}(\text{S})\text{NHR}^k$, $-\text{NR}^k\text{C}(\text{O})\text{NH}_2$, $-\text{NR}^k\text{C}(\text{S})\text{NH}_2$, $-\text{NR}^k\text{C}(\text{O})\text{NHR}^k$, $-\text{NR}^k\text{C}(\text{S})\text{NHR}^k$, $-\text{NHC}(\text{O})\text{NR}^k\text{R}^k$, $-\text{NHC}(\text{S})\text{NR}^k\text{R}^k$, $-\text{NR}^k\text{C}(\text{O})\text{NR}^k\text{R}^k$, $-\text{NR}^k\text{C}(\text{S})\text{NR}^k\text{R}^k$, $-\text{NHS}(\text{O})_2\text{NHR}^k$, $-\text{NR}^k\text{S}(\text{O})_2\text{NH}_2$, $-\text{NR}^k\text{S}(\text{O})_2\text{NHR}^k$, $-\text{NHS}(\text{O})_2\text{NR}^k\text{R}^k$, $-\text{NR}^k\text{S}(\text{O})_2\text{NR}^k\text{R}^k$, $-\text{NHR}^k$, $-\text{NR}^k\text{R}^k$, $-\text{R}^h$, $-\text{R}^i$, and $-\text{R}^j$;

wherein R^k , R^m , and R^n at each occurrence are independently selected from the group consisting of R^h , R^i , and R^j , or R^m and R^n combine with the nitrogen to which they are attached form a 5-7 membered heterocycloalkyl or a 5 or 7 membered nitrogen containing heteroaryl, wherein the 5-7 membered heterocycloalkyl or 5 or 7 membered nitrogen containing heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, OR^u , $-\text{SR}^u$, $-\text{NHR}^u$, $-\text{NR}^u\text{R}^u$, $-\text{R}^x$, and $-\text{R}^y$;

wherein each R^h is independently lower alkyl optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of fluoro, $-\text{OH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{S})\text{OH}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{S})\text{NH}_2$, $-\text{S}(\text{O})_2\text{NH}_2$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{S})\text{NH}_2$, $-\text{NHS}(\text{O})_2\text{NH}_2$, $-\text{C}(\text{NH})\text{NH}_2$, $-\text{OR}^t$, $-\text{SR}^t$, $-\text{OC}(\text{O})\text{R}^t$, $-\text{OC}(\text{S})\text{R}^t$, $-\text{C}(\text{O})\text{R}^t$, $-\text{C}(\text{S})\text{R}^t$, $-\text{C}(\text{O})\text{OR}^t$,

-C(S)ORⁱ, -S(O)Rⁱ, -S(O)₂Rⁱ, -C(O)NHRⁱ, -C(S)NHRⁱ, -C(O)NRⁱRⁱ, -C(S)NRⁱRⁱ, -S(O)₂NHRⁱ,
 -S(O)₂NRⁱRⁱ, -C(NH)NHRⁱ, -C(NH)NR^sRⁱ, -NHC(O)Rⁱ, -NHC(S)Rⁱ, -NRⁱC(O)Rⁱ, -NRⁱC(S)Rⁱ,
 -NHS(O)₂Rⁱ, -NRⁱS(O)₂Rⁱ, -NHC(O)NHRⁱ, -NHC(S)NHRⁱ, -NRⁱC(O)NH₂, -NRⁱC(S)NH₂,
 -NRⁱC(O)NHRⁱ, -NRⁱC(S)NHRⁱ, -NHC(O)NRⁱRⁱ, -NHC(S)NRⁱRⁱ, -NRⁱC(O)NRⁱRⁱ,
 -NRⁱC(S)NRⁱRⁱ, -NHS(O)₂NHRⁱ, -NRⁱS(O)₂NH₂, -NRⁱS(O)₂NHRⁱ, -NHS(O)₂NRⁱRⁱ,
 -NRⁱS(O)₂NRⁱRⁱ, -NHRⁱ, -NRⁱRⁱ, -Rⁱ, and -R^j;

wherein each Rⁱ is independently selected from the group consisting of lower alkenyl and lower alkynyl, wherein lower alkenyl or lower alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of fluoro, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -ORⁱ, -SRⁱ, -OC(O)Rⁱ, -OC(S)Rⁱ, -C(O)Rⁱ, -C(S)Rⁱ, -C(O)ORⁱ, -C(S)ORⁱ, -S(O)Rⁱ, -S(O)₂Rⁱ, -C(O)NHRⁱ, -C(S)NHRⁱ, -C(O)NRⁱRⁱ, -C(S)NRⁱRⁱ, -S(O)₂NHRⁱ, -S(O)₂NRⁱRⁱ, -C(NH)NHRⁱ, -C(NH)NR^sRⁱ, -NHC(O)Rⁱ, -NHC(S)Rⁱ, -NRⁱC(O)Rⁱ, -NRⁱC(S)Rⁱ, -NHS(O)₂Rⁱ, -NRⁱS(O)₂Rⁱ, -NHC(O)NHRⁱ, -NHC(S)NHRⁱ, -NRⁱC(O)NH₂, -NRⁱC(S)NH₂, -NRⁱC(O)NHRⁱ, -NRⁱC(S)NHRⁱ, -NHC(O)NRⁱRⁱ, -NHC(S)NRⁱRⁱ, -NRⁱC(O)NRⁱRⁱ, -NRⁱC(S)NRⁱRⁱ, -NHS(O)₂NHRⁱ, -NRⁱS(O)₂NH₂, -NRⁱS(O)₂NHRⁱ, -NHS(O)₂NRⁱRⁱ, -NRⁱS(O)₂NRⁱRⁱ, -NHRⁱ, -NRⁱRⁱ, and -R^j;

wherein each Rⁱ is independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -ORⁱ, -SRⁱ, -OC(O)Rⁱ, -OC(S)Rⁱ, -C(O)Rⁱ, -C(S)Rⁱ, -C(O)ORⁱ, -C(S)ORⁱ, -S(O)Rⁱ, -S(O)₂Rⁱ, -C(O)NHRⁱ, -C(S)NHRⁱ, -C(O)NRⁱRⁱ, -C(S)NRⁱRⁱ, -S(O)₂NHRⁱ, -S(O)₂NRⁱRⁱ, -C(NH)NHRⁱ, -C(NH)NR^sRⁱ, -NHC(O)Rⁱ, -NHC(S)Rⁱ, -NRⁱC(O)Rⁱ, -NRⁱC(S)Rⁱ, -NHS(O)₂Rⁱ, -NRⁱS(O)₂Rⁱ, -NHC(O)NHRⁱ, -NHC(S)NHRⁱ, -NRⁱC(O)NH₂, -NRⁱC(S)NH₂, -NRⁱC(O)NHRⁱ, -NRⁱC(S)NHRⁱ, -NHC(O)NRⁱRⁱ, -NHC(S)NRⁱRⁱ, -NRⁱC(O)NRⁱRⁱ, -NRⁱC(S)NRⁱRⁱ, -NHS(O)₂NHRⁱ, -NRⁱS(O)₂NH₂, -NRⁱS(O)₂NHRⁱ, -NHS(O)₂NRⁱRⁱ, -NRⁱS(O)₂NRⁱRⁱ, -NHRⁱ, -NRⁱRⁱ, cycloalkylamino, and -R^k;

wherein each Rⁱ, R^s, and Rⁱ at each occurrence are independently selected from the group consisting of lower alkyl, C₃₋₆ alkenyl, C₃₋₆ alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of -R^y, fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that

any substitution of the lower alkyl carbon bound to any O, S, or N, of -ORⁱ, -SRⁱ, -C(O)ORⁱ, -C(S)ORⁱ, -C(O)NHRⁱ, -C(S)NHRⁱ, -C(O)NRⁱRⁱ, -C(S)NRⁱRⁱ, -S(O)₂NHRⁱ, -S(O)₂NRⁱRⁱ, -C(NH)NHRⁱ, -NRⁱC(O)Rⁱ, -NRⁱC(S)Rⁱ, -NRⁱS(O)₂Rⁱ, -NHC(O)NHRⁱ, -NHC(S)NHRⁱ, -NRⁱC(O)NH₂, -NRⁱC(S)NH₂, -NRⁱC(O)NHRⁱ, -NRⁱC(S)NHRⁱ, -NHC(O)NRⁱRⁱ, -NHC(S)NRⁱRⁱ, -NRⁱC(O)NRⁱRⁱ, -NRⁱC(S)NRⁱRⁱ, -NHS(O)₂NHRⁱ, -NRⁱS(O)₂NH₂, -NRⁱS(O)₂NHRⁱ, -NHS(O)₂NRⁱRⁱ, -NRⁱS(O)₂NRⁱRⁱ, -NHRⁱ, or -NRⁱRⁱ is selected from the group consisting of fluoro and -R^y, and wherein C₃₋₆ alkenyl or C₃₋₆ alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of -R^y, fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the C₃₋₆ alkenyl or C₃₋₆ alkynyl carbon bound to any O, S, or N, of -ORⁱ, -SRⁱ, -C(O)ORⁱ, -C(S)ORⁱ, -C(O)NHRⁱ, -C(S)NHRⁱ, -C(O)NRⁱRⁱ, -C(S)NRⁱRⁱ, -S(O)₂NHRⁱ, -S(O)₂NRⁱRⁱ, -C(NH)NHRⁱ, -NRⁱC(O)Rⁱ, -NRⁱC(S)Rⁱ, -NRⁱS(O)₂Rⁱ, -NHC(O)NHRⁱ, -NHC(S)NHRⁱ, -NRⁱC(O)NH₂, -NRⁱC(S)NH₂, -NRⁱC(O)NHRⁱ, -NRⁱC(S)NHRⁱ, -NHC(O)NRⁱRⁱ, -NHC(S)NRⁱRⁱ, -NRⁱC(O)NRⁱRⁱ, -NRⁱC(S)NRⁱRⁱ, -NHS(O)₂NHRⁱ, -NRⁱS(O)₂NH₂, -NRⁱS(O)₂NHRⁱ, -NHS(O)₂NRⁱRⁱ, -NRⁱS(O)₂NRⁱRⁱ, -NHRⁱ, or -NRⁱRⁱ is selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, and -R^y, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, or R^s and R^t combine with the nitrogen to which they are attached form a 5-7 membered heterocycloalkyl or a 5 or 7 membered nitrogen containing heteroaryl, wherein the 5-7 membered heterocycloalkyl or 5 or 7 membered nitrogen containing heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, -NO₂, -CN, -OH, -NH₂, OR^u, -SR^u, -NHR^u, -NR^uR^u, -R^x, and -R^y;

wherein each R^u is independently selected from the group consisting of lower alkyl, C₃₋₆ alkenyl, C₃₋₆ alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein lower alkyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of -R^y, fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the lower alkyl carbon bound to the O of -OR^u, S of -SR^u, or N of -NHR^u is fluoro or -R^y, and wherein C₃₋₆ alkenyl or C₃₋₆ alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4

or 5, also 1, 2, or 3 substituents selected from the group consisting of -R^y, fluoro, -OH, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the C₃₋₆ alkenyl or C₃₋₆ alkynyl carbon bound to the O of -OR^u, S of -SR^u, or N of -NHR^u is fluoro, lower alkyl, fluoro substituted lower alkyl, or -R^y, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

wherein each R^x is selected from the group consisting of lower alkyl, lower alkenyl and lower alkynyl, wherein lower alkyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of -R^y, fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein lower alkenyl or lower alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of -R^y, fluoro, -OH, -NH₂, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

wherein each R^y is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

[0115] In some embodiments, all occurrences of optionally substituted lower alkyl, optionally substituted C₂₋₆ alkyl, optionally substituted lower alkenyl, or optionally substituted lower alkynyl are optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of fluoro, -NO₂, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -OC(O)R^{1a}, -OC(S)R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -C(O)OR^{1a}, -C(S)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -C(NH)NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -NR^{1a}C(O)NR^{1a}R^{1a}, -NR^{1a}C(S)NR^{1a}R^{1a}, -NR^{1a}S(O)₂NR^{1a}R^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of halogen, -NO₂, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -OC(O)R^{1a},

-OC(S)R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -C(O)OR^{1a}, -C(S)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -C(NH)NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -NR^{1a}C(O)NR^{1a}R^{1a}, -NR^{1a}C(S)NR^{1a}R^{1a}, -NR^{1a}S(O)₂NR^{1a}R^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, -R^{1b}, and lower alkyl optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and -R^{1b}, and all occurrences of optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted 5-7 membered heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted 5 or 7 membered nitrogen containing heteroaryl are optionally substituted with one or more, also 1, 2, or 3 groups or substituents selected from the group consisting of halogen, -NO₂, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -OC(O)R^{1a}, -OC(S)R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -C(O)OR^{1a}, -C(S)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -C(NH)NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -NR^{1a}C(O)NR^{1a}R^{1a}, -NR^{1a}C(S)NR^{1a}R^{1a}, -NR^{1a}S(O)₂NR^{1a}R^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, -R^{1b}, and lower alkyl optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and -R^{1b}, wherein R^{1a} is selected from the group consisting of hydrogen, provided, however, that hydrogen is not bound to any of C(S), C(O), S(O), or S(O)₂ of -OC(O)R^{1a}, -OC(S)R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -S(O)R^{1a}, or -S(O)₂R^{1a}, -R^{1b}, and lower alkyl optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and -R^{1b}, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -C(O)OR^{1a}, -C(S)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -C(NH)NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -NR^{1a}C(O)NR^{1a}R^{1a}, -NR^{1a}C(S)NR^{1a}R^{1a}, or -NR^{1a}S(O)₂NR^{1a}R^{1a}, is fluoro or -R^{1b}, and wherein -R^{1b} is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of halogen, -CN, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

[0116] In some embodiments, all occurrences of optionally substituted lower alkyl, optionally substituted C₂₋₆ alkyl, optionally substituted lower alkenyl, or optionally substituted lower alkynyl are optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of fluoro, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and

heteroaryl are optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of halogen, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, -R^{1b}, and lower alkyl optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and -R^{1b}, and all occurrences of optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted 5-7 membered heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted 5 or 7 membered nitrogen containing heteroaryl are optionally substituted with one or more, also 1, 2, or 3 groups or substituents selected from the group consisting of halogen, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, -R^{1b}, and lower alkyl optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and -R^{1b}, wherein R^{1a} is selected from the group consisting of hydrogen, provided, however, that hydrogen is not bound to any of C(S), C(O), S(O), or S(O)₂ of -C(O)R^{1a}, -C(S)R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -S(O)R^{1a}, or -S(O)₂R^{1a}, -R^{1b}, and lower alkyl optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of fluoro, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and -R^{1b}, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, or -NR^{1a}S(O)₂R^{1a}, is fluoro or -R^{1b}, and wherein -R^{1b} is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with one or more, also 1, 2 or 3 groups or substituents selected from the group consisting of halogen, -CN, -OH, -NH₂, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

[0117] "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, for example, in the description of compounds of Formula III, including descriptions of substituted cycloalkyl, cycloheteroalkyl, aryl and heteroaryl, 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.

[0118] "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, for example, in the description of compounds of Formula III, including descriptions of substituted cycloalkyl, cycloheteroalkyl, aryl and heteroaryl, 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.

[0119] "Amino" or "amine" denotes the group $-NH_2$. "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.

[0120] A "nitrogen protecting group" is a chemical group covalently bound to a nitrogen atom of a compound that is used to protect the nitrogen from reaction during a synthetic step. The nitrogen protecting group may be added to a compound and removed in a subsequent step by methods known to those of skill in the art. Nitrogen protecting groups include, without limitation, carbamates,

amides, N-sulfonyl derivatives, groups of formula -C(O)OR, wherein R is, for example, methyl, ethyl, t-butyl, benzyl, phenylethyl, CH₂=CHCH₂-, and the like, groups of the formula -C(O)R', wherein R' is, for example, methyl, phenyl, trifluoromethyl, and the like, groups of the formula -SO₂R", wherein R" is, for example, tolyl, phenyl, trifluoromethyl, 2,2,5,7,8-pentamethylchroman-6-yl, 2,3,6-trimethyl-4-methoxyphenyl, and the like, and silanyl containing groups, such as 2-trimethylsilylethoxymethyl, t-butyldimethylsilyl, triisopropylsilyl, and the like. Other suitable nitrogen protecting groups may be found in texts such as T. W. Greene & P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991.

[0121] 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.

[0122] The term "pharmaceutically acceptable" indicates that the indicated material does not have properties that would cause a reasonably prudent medical or veterinary practitioner to avoid administration of the material to a subject, 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.

[0123] In the present context, the term "therapeutically effective" or "effective amount" indicates that the materials or amount of material is effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or condition, and/or to prolong the survival of the subject being treated.

[0124] 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 a protein kinase. For example, an agonist or antagonist of a particular biomolecule modulates the activity of that biomolecule, e.g., an enzyme, by either increasing (e.g. agonist, activator), or decreasing (e.g. antagonist, inhibitor) the activity of the biomolecule, such as an enzyme. Such activity is typically indicated in terms of an inhibitory concentration (IC₅₀) or excitation concentration (EC₅₀) of the compound for an inhibitor or activator, respectively, with respect to, for example, an enzyme.

[0125] In the context of the use, testing, or screening of compounds that are or may be modulators, the term "contacting" means that the compound(s) are caused to be in sufficient proximity to a particular molecule, complex, cell, tissue, organism, or other specified material that potential binding interactions and/or chemical reaction between the compound and other specified material can occur.

[0126] The present invention concerns compounds of Formula III and all sub-generic formulae thereof including compounds of Formula IIIa-m and all sub-generic formulae thereof, including all salts, prodrugs, tautomers, and isomers, that are modulators of protein kinases, for example without limitation, the compounds are modulators of at least one of the kinases selected from the group consisting of B-Raf, c-Raf-1, Fms, Jnk1, Jnk2, Jnk3, Kit, and any mutations of these kinases, and the use of such compounds in the treatment of diseases or conditions.

II. Kinase targets and indications of the invention

[0127] Protein kinases play key roles in propagating biochemical signals in diverse biological pathways. More than 500 kinases have been described, and specific kinases have been implicated in a wide range of diseases or conditions including, for example without limitation, cancer, cardiovascular disease, inflammatory disease, neurological disease, and other diseases and conditions. As such, kinases represent important control points for small molecule therapeutic intervention. Specific target protein kinases contemplated by the present invention follow:

[0128] **B-Raf:** Target kinase B-Raf (i.e., v-raf murine sarcoma viral oncogene homolog B1) is a 84.4 kDa serine/threonine kinase encoded by chromosome 7q34 (symbol: BRAF). The mature protein comprises RBD (i.e., Ras binding domain), C1 (i.e., protein kinase C conserved region 1) and STK (i.e., serine/threonine kinase) domains. Target kinase B-Raf includes any mutations of B-Raf, such as Val<600> to Glu<600> (V600E) mutant.

[0129] Indications for modulation of B-Raf activity, including B-Raf V600E activity, for the treatment of pathologic states include, but are not limited to, neurologic diseases such as ischemic stroke, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease; neoplastic diseases including, but not limited to, melanoma, glioma, sarcoma, carcinoma (e.g. lung, breast, pancreatic, renal), lymphoma (e.g. histiocytic lymphoma) and cancer of the thyroid, lung (e.g. small cell lung cancer), liver, breast, ovary and colon, neurofibromatosis, myelodysplastic syndrome, leukemia, tumor angiogenesis; pain of neuropathic or inflammatory origin, including acute pain, chronic pain, and migraine; cardiovascular diseases including heart failure, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, reperfusion injury; inflammation including, but not limited to, psoriasis, polycystic kidney disease (PKD), arthritis and autoimmune diseases and conditions, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease (IBD); immunodeficiency diseases, organ transplant rejection, graft versus host disease; renal or prostatic diseases including diabetic nephropathy, nephrosclerosis, glomerulonephritis, prostate hyperplasia; metabolic disorders,

obesity; infection, including, but not limited to *Helicobacter pylori* and *Influenza virus*, fever, sepsis; pulmonary diseases including chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS); genetic developmental diseases such as Noonan's syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), leopard syndrome, cardio-faciocutaneous syndrome (CFC), and neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases.

[0130] **c-Raf-1:** Target kinase c-Raf-1 (i.e., v-raf murine sarcoma viral oncogene homolog 1) is a 73.0 kDa STK encoded by chromosome 3p25 (symbol: RAF1). c-Raf-1 can be targeted to the mitochondria by BCL2 (i.e., oncogene B-cell leukemia 2) which is a regulator of apoptotic cell death. Active c-Raf-1 improves BCL2-mediated resistance to apoptosis, and c-Raf-1 phosphorylates BAD (i.e., BCL2-binding protein). c-Raf-1 is implicated in carcinomas, including colorectal, ovarian, lung and renal cell carcinoma. C-Raf-1 is also implicated as an important mediator of tumor angiogenesis (Hood *et al.*, 2002, *Science* 296, 2404). C-Raf-1 inhibitors may also be useful for the treatment of acute myeloid leukemia and myelodysplastic syndromes (Crump, *Curr Pharm Des* 2002, 8(25):2243-8). Raf-1 activators may be useful as treatment for neuroendocrine tumors, such as medullary thyroid cancer, carcinoid, small cell lung cancer and pheochromocytoma (Kunnimalaiyaan *et al.*, *Anticancer Drugs* 2006, 17(2):139-42).

[0131] **Fms:** Target kinase Fms (i.e., feline McDonough sarcoma) is a member of the family of genes originally isolated from the Susan McDonough strain of feline sarcoma viruses. Fms is a transmembrane tyrosine kinase of 108.0 kDa coded by chromosome 5q33.2-q33.3 (symbol: CSF1R). The structure of the transmembrane receptor Fms comprises two Ig-like domains, a IgC2-like domain, two additional Ig-like domains, a TM domain, and the TK domain.

[0132] The presence of c-fms has been associated with a number of different types of diseases. Fms has been associated with immune disorders, including rheumatoid arthritis, systemic lupus erythematosus (SLE), Wegener's granulomatosis, and transplant rejection, inflammatory diseases including Chronic Obstructive Pulmonary Disease (COPD), emphysema, and atherosclerosis, metabolic disorders, including insulin resistance, hyperglycemia, and lipolysis, disorders of bone structure or mineralization, including osteoporosis, increased risk of fracture, hypercalcemia, and bone metastases, kidney diseases, including nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications, and hypertrophy and cancers, including multiple myeloma, acute myeloid leukemia, chronic myeloid leukemia (CML), breast cancer, and ovarian cancer.

[0133] **Jnk1:** Target Jnk1 (i.e., c-Jun kinase 1) is a 48.3 kDa serine/threonine kinase encoded by chromosome 10q11.22 (symbol: MAPK8), also known as mitogen-activated protein kinase 8. Jnk1 is

a mitogen-activated protein kinase (i.e., MAPK) which form a family of serine-threonine protein kinases that participate in a major signaling system by which cells transduce extracellular stimuli into intracellular responses. Jnk1 is implicated in type 1 diabetes, type 2 diabetes, metabolic syndrome, obesity and hepatic steatosis.

[0134] **Jnk2:** Target kinase Jnk2 (i.e., c-Jun kinase 2) is 48.1 kDa serine/threonine kinase encoded by chromosome 5q35 (symbol: MAPK9). Jnk2 is implicated in atherosclerosis.

[0135] **Jnk3:** Target kinase Jnk3 (i.e., c-Jun kinase 3) is 52.6 kDa serine/threonine kinase encoded by chromosome 4q21-q22 (symbol: MAPK10). Jnk3 inhibitors are potential therapeutics for the treatment of Inflammatory diseases including autoimmune diseases such as rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosus, Sjogren's Syndrome, psoriasis and multiple sclerosis, airway inflammatory diseases such as asthma, allergy, pulmonary fibrosis, and chronic obstructive pulmonary disease, and inflammation in other organs, such as CNS inflammation, pancreatitis, nephritis, and hepatitis; neurologic diseases such as stroke, cerebrovascular ischemia, and neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Huntington's disease; and neoplastic diseases such as prostate tumors and myeloid leukemia.

[0136] **Kit:** Target kinase Kit (i.e., feline Hardy-Zuckerman 4 sarcoma viral oncogene) is a 109.9 kDa transmembrane tyrosine kinase encoded by chromosome 4q12 (symbol: KIT). Receptor protein tyrosine kinases (RPTKs) regulate key signal transduction cascades that control cellular growth and proliferation. The Stem Cell Factor (SCF) receptor Kit is a type III transmembrane RPTK that includes five extracellular immunoglobulin (IG) domains, a single transmembrane domain, and a split cytoplasmic kinase domain separated by a kinase insert segment. Kit plays an important role in the development of melanocytes, mast, germ, and hematopoietic cells.

[0137] Aberrant expression and/or activation of Kit has been implicated in a variety of pathologic states. Kit has been associated with 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.

III. Kinase Activity Assays

[0138] A number of different assays for kinase activity can be utilized for assaying for active modulators and/or determining specificity of a modulator for a particular kinase or group of kinases. In addition to the assays mentioned in the Examples below, one of ordinary skill in the art will know of other assays that can be utilized and can modify an assay for a particular application. For example, numerous papers concerning kinases describe assays that can be used. When assayed for kinase activity, preferred compounds of the present invention (i.e., compounds of Formula III) will have an IC_{50} or EC_{50} of less than 10 μ M, also less than 1 μ M, also less than 100 nM, also less than 10 nM or less than 1 nM.

IV. Organic Synthetic Techniques

[0139] A wide array of organic synthetic techniques exist in the art to prepare compounds of Formula III. Many of these organic synthetic methods are described in detail in standard reference sources utilized by those skilled in the art. One example of such a reference is March, 1994, *Advanced Organic Chemistry; Reactions, Mechanisms and Structure*, New York, McGraw Hill.

V. Alternative Compound Forms or Derivatives

[0140] Compounds contemplated herein are described with reference to both generic formulae and specific compounds. In addition, invention compounds may exist in a number of different forms or derivatives, all within the scope of the present invention. These include, for example, tautomers, stereoisomers, racemic mixtures, regioisomers, salts, prodrugs (e.g., carboxylic acid esters), solvated forms, different crystal forms or polymorphs, and active metabolites.

(a) Tautomers, Stereoisomers, Regioisomers, and Solvated Forms

[0141] It is understood that some compounds may exhibit tautomerism. In such cases, the formulae provided herein expressly depict only one of the possible tautomeric forms. It is therefore to be understood that the formulae provided herein are intended to represent any tautomeric form of the depicted compounds and are not to be limited merely to the specific tautomeric form depicted by the drawings of the formulae.

[0142] Likewise, some of the compounds according to the present invention may exist as stereoisomers, i.e. having the same atomic connectivity of covalently bonded atoms yet differing in the spatial orientation of the atoms. For example, compounds may be optical stereoisomers, which contain one or more chiral centers, and therefore, may exist in two or more stereoisomeric forms (e.g. enantiomers or diastereomers). Thus, such compounds may be present as single stereoisomers (i.e.,

essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. As another example, stereoisomers include geometric isomers, such as *cis*- or *trans*-orientation of substituents on adjacent carbons of a double bond. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Unless specified to the contrary, all such stereoisomeric forms are included within the formulae provided herein.

[0143] In some embodiments, a chiral compound of the present invention is in a form that contains at least 80% of a single isomer (60% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), or at least 85% (70% e.e. or d.e.), 90% (80% e.e. or d.e.), 95% (90% e.e. or d.e.), 97.5% (95% e.e. or d.e.), or 99% (98% e.e. or d.e.). As generally understood by those skilled in the art, an optically pure compound having one chiral center is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. In some embodiments, the compound is present in optically pure form.

[0144] For compounds in which synthesis involves addition of a single group at a double bond, particularly a carbon-carbon double bond, the addition may occur at either of the double bond-linked atoms. For such compounds, the present invention includes both such regioisomers.

[0145] Additionally, the formulae are intended to cover solvated as well as unsolvated forms of the identified structures. For example, the indicated structures include both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with a suitable solvent such as isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine.

(b) Prodrugs and Metabolites

[0146] In addition to the present formulae and compounds described herein, the invention also includes prodrugs (generally pharmaceutically acceptable prodrugs), active metabolic derivatives (active metabolites), and their pharmaceutically acceptable salts.

[0147] Prodrugs are compounds or pharmaceutically acceptable salts thereof which, when metabolized under physiological conditions or when converted by solvolysis, yield the desired active compound. Prodrugs include, without limitation, esters, amides, carbamates, carbonates, ureides, solvates, or hydrates of the active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide one or more advantageous handling, administration, and/or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolism, the ester group is cleaved to yield the active drug. Also, some prodrugs are activated

enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound.

[0148] In this context, a common example or a prodrug is an alkyl ester of a carboxylic acid. Relative to compounds of Formula III, further examples include, without limitation, an amide or carbamate derivative at the 1-position nitrogen of the azaindole core.

[0149] As described in *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, CA, 2001), prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. Generally, bioprecursor prodrugs are compounds that are inactive or have low activity compared to the corresponding active drug compound, that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity. Typically, the formation of active drug compound involves a metabolic process or reaction that is one of the follow types:

[0150] Oxidative reactions: Oxidative reactions are exemplified without limitation to reactions such as oxidation of alcohol, carbonyl, and acid functionalities, hydroxylation of aliphatic carbons, hydroxylation of alicyclic carbon atoms, oxidation of aromatic carbon atoms, oxidation of carbon-carbon double bonds, oxidation of nitrogen-containing functional groups, oxidation of silicon, phosphorus, arsenic, and sulfur, oxidative N-dealkylation, oxidative O- and S-dealkylation, oxidative deamination, as well as other oxidative reactions.

[0151] Reductive reactions: Reductive reactions are exemplified without limitation to reactions such as reduction of carbonyl functionalities, reduction of alcohol functionalities and carbon-carbon double bonds, reduction of nitrogen-containing function groups, and other reduction reactions.

[0152] Reactions without change in the oxidation state: Reactions without change in the state of oxidation are exemplified without limitation to reactions such as hydrolysis of esters and ethers, hydrolytic cleavage of carbon-nitrogen single bonds, hydrolytic cleavage of non-aromatic heterocycles, hydration and dehydration at multiple bonds, new atomic linkages resulting from dehydration reactions, hydrolytic dehalogenation, removal of hydrogen halide molecule, and other such reactions.

[0153] Carrier prodrugs are drug compounds that contain a transport moiety, e.g., that improves uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, the prodrug and any release transport moiety are acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the

release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, e.g., certain polymers or other moieties, such as cyclodextrins. (See, e.g., Cheng et al., U.S. Patent Publ. No. 20040077595, App. No. 10/656,838, incorporated herein by reference). Such carrier prodrugs are often advantageous for orally administered drugs. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (e.g., stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of hydroxyl groups with lipophilic carboxylic acids, or of carboxylic acid groups with alcohols, e.g., aliphatic alcohols. Wermuth, *supra*.

[0154] Prodrugs may proceed from prodrug form to active form in a single step or may have one or more intermediate forms which may themselves have activity or may be inactive.

[0155] Metabolites, e.g., active metabolites overlap with prodrugs as described above, e.g., bioprecursor prodrugs. Thus, such metabolites are pharmacologically active compounds or compounds that further metabolize to pharmacologically active compounds that are derivatives resulting from metabolic process in the body of a subject. Of these, active metabolites are such pharmacologically active derivative compounds. For prodrugs, the prodrug compound is generally inactive or of lower activity than the metabolic product. For active metabolites, the parent compound may be either an active compound or may be an inactive prodrug.

[0156] Prodrugs and active metabolites may be identified using routine techniques known in the art. See, e.g., Bertolini et al, 1997, *J Med Chem* 40:2011-2016; Shan et al., *J Pharm Sci* 86:756-757; Bagshawe, 1995, *Drug Dev Res* 34:220-230; Wermuth, *supra*.

(c) Pharmaceutically acceptable salts

[0157] Compounds can be formulated as or be in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts are non-toxic in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

[0158] Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, chloride, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and

quate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

[0159] Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chlorprocaine, choline, diethanolamine, ethanolamine, *t*-butylamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see *Remington's Pharmaceutical Sciences*, 19th ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. Such salts can be prepared using the appropriate corresponding bases.

[0160] Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free-base form of a compound can be dissolved in a suitable solvent, such as an aqueous or aqueous-alcohol solution containing the appropriate acid and then isolated by evaporating the solution. In another example, a salt can be prepared by reacting the free base and acid in an organic solvent.

[0161] Thus, for example, if the particular compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as *p*-toluenesulfonic acid or ethanesulfonic acid, or the like.

[0162] Similarly, if the particular compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as *L*-glycine, *L*-lysine and *L*-arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as hydroxyethylpyrrolidine, piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium. Further examples of pharmaceutically acceptable salts of compounds of Formula I include, without limitation, the mono-sodium and bis-potassium salts thereof.

[0163] The pharmaceutically acceptable salt of the different compounds may be present as a complex. Examples of complexes include 8-chlorotheophylline complex (analogous to, *e.g.*, dimenhydrinate: diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

[0164] Unless specified to the contrary, specification of a compound herein includes pharmaceutically acceptable salts of such compound.

(d) Polymorphic forms

[0165] In the case of agents that are solids, it is understood by those skilled in the art that the compounds and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

VI. Administration

[0166] 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.

[0167] Suitable dosage forms, in part, depend upon the use or the route of administration, for example, oral, transdermal, transmucosal, inhalant or by injection (parenteral). Such dosage forms should allow the compound to reach target cells. Other factors are well known in the art, and include considerations such as toxicity and dosage forms that retard the compound or composition from exerting its effects. Techniques and formulations generally may be found in *The Science and Practice of Pharmacy*, 21st edition, Lippincott, Williams and Wilkins, Philadelphia, PA, 2005 (hereby incorporated by reference herein).

[0168] Compounds of the present invention, *i.e.* Formula III, can be formulated as pharmaceutically acceptable salts.

[0169] Carriers or excipients can be used to produce compositions. The carriers or excipients can be chosen to facilitate administration of the compound. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. Examples of physiologically compatible solvents include sterile solutions of water for injection (WFI), saline solution, and dextrose.

[0170] The compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, transmucosal, rectal, transdermal, or inhalant. Oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

[0171] For inhalants, compounds of the invention may be formulated as dry powder or a suitable solution, suspension, or aerosol. Powders and solutions may be formulated with suitable additives known in the art. For example, powders may include a suitable powder base such as lactose or starch, and solutions may comprise propylene glycol, sterile water, ethanol, sodium chloride and other additives, such as acid, alkali and buffer salts. Such solutions or suspensions may be administered by inhaling via spray, pump, atomizer, or nebulizer, and the like. The compounds of the invention may also be used in combination with other inhaled therapies, for example corticosteroids such as fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide, budesonide, and mometasone furoate; beta agonists such as albuterol, salmeterol, and formoterol; anticholinergic agents such as ipratropium bromide or tiotropium; vasodilators such as treprostinil and iloprost; enzymes such as DNAase; therapeutic proteins; immunoglobulin antibodies; an oligonucleotide, such as single or double stranded DNA or RNA, siRNA; antibiotics such as tobramycin; muscarinic receptor antagonists; leukotriene antagonists; cytokine antagonists; protease inhibitors; cromolyn sodium; nedocril sodium; and sodium cromoglycate.

[0172] Pharmaceutical preparations for oral use can be obtained, for example, by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid, or a salt thereof such as sodium alginate.

[0173] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain, for example, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0174] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin ("gelcaps"), as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

[0175] Alternatively, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and/or subcutaneous. For injection, the compounds of the invention are formulated in sterile liquid solutions, preferably in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

[0176] Administration can also be by transmucosal, topical, or transdermal means. For transmucosal, topical or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays or suppositories (rectal or vaginal). The topical compositions of this invention are formulated preferably as oils, creams, lotions, ointments and the like by choice of appropriate carriers known in the art. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C₁₂). The preferred carriers are those in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Creams for topical application are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount solvent (*e.g.*, an oil), is admixed. Additionally, administration by transdermal means may comprise a transdermal patch or dressing such as a bandage impregnated with an active ingredient and optionally one or more carriers or diluents known in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[0177] The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC₅₀, the biological half-life of the compound, the age, size, and weight of the subject, and the disorder associated with the subject. The importance of these and other factors are well known to those of ordinary skill in the art. Generally, a

dose will be between about 0.01 and 50 mg/kg, preferably 0.1 and 20 mg/kg of the subject being treated. Multiple doses may be used.

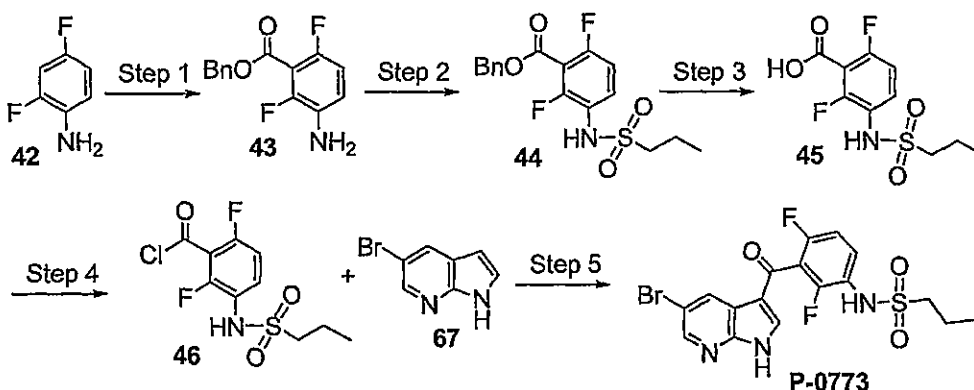
EXAMPLES

[0178] Examples related to the present invention are described below. In most cases, alternative techniques can be used. The examples are intended to be illustrative and are not limiting or restrictive to the scope of the invention. In some examples, the mass spectrometry result indicated for a compound may have more than one value due to the isotope distribution of an atom in the molecule, such as a compound having a bromo or chloro substituent.

Example 1: Synthesis of propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide P-0773 and related compounds.

[0179] Compound P-0773 was synthesized in five steps from 2,4-difluoro-phenylamine 42 as shown in Scheme 13.

Scheme 13



Step 1 – Preparation of 3-amino-2,6-difluoro-benzoic acid benzyl ester (43):

[0180] To 2,4-difluoro-phenylamine (42, 5.11 mL, 50.7 mmol) in tetrahydrofuran (250 mL), cooled with dry ice/acetone bath under an atmosphere of nitrogen, was added n-butyllithium (1.60 M in hexane, 34.0 mL, 54.4 mmol) slowly. After 30 minutes, 1,2-Bis-(chloro-dimethyl-silanyl)-ethane (11.5 g, 53.4 mmol) dissolved in tetrahydrofuran (40.0 mL) was added to the reaction slowly. After 1 hour, n-butyllithium (1.60 M in hexane, 31.9 mL, 51.0 mmol) was added slowly to the reaction. The reaction was stirred at -78 °C for 30 minutes and then allowed to warm to room temperature over 40 minutes. The reaction was cooled to -78 °C, followed by addition of n-butyllithium (1.60 M in hexane, 35.1 mL, 56.2 mmol) slowly. After 70 minutes, benzyl chloroformate (7.97 mL, 55.8 mmol) was added to the reaction. The reaction mixture was stirred at -78 °C overnight followed by addition of 2 N HCl (120 mL). The reaction was allowed to warm to room temperature for 2 hours. The

organic layer was separated. The aqueous layer was basified with potassium carbonate and extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous sodium sulfate, filtrated and concentrated. The desired compound was isolated by silica gel column chromatography (ethyl acetate/hexane 20%) to give a colorless oil (43, 10.6 g, 79.7%). MS(ESI) $[M+H]^+ = 264.1$.

Step 2 – Preparation of 2,6-difluoro-3-(propane-1-sulfonylamino)-benzoic acid benzyl ester (44):

[0181] To 3-amino-2,6-difluoro-benzoic acid benzyl ester (43, 6.00 g, 22.8 mmol) in methylene chloride (150 mL) was added pyridine (2.76 mL, 34.2 mmol) and propane-1-sulfonyl chloride (3.80 mL, 33.8 mmol). The reaction was stirred at room temperature overnight. Then the reaction was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated and concentrated. The desired compound was isolated with silica gel column chromatography to give a colorless oil (44, 7.0 g, 83.1%). MS(ESI) $[M+H]^+ = 370.1$.

Step 3 – Preparation of 2,6-difluoro-3-(propane-1-sulfonylamino)-benzoic acid (45):

[0182] To 2,6-difluoro-3-(propane-1-sulfonylamino)-benzoic acid benzyl ester (44, 2.0 g, mmol) in methanol (30 mL) was added 20% palladium hydroxide on carbon (100 mg). The reaction was stirred under hydrogen at 1 atm for 15 minutes. The reaction was filtrated and concentrated to give white solid 45 that was used in the next step.

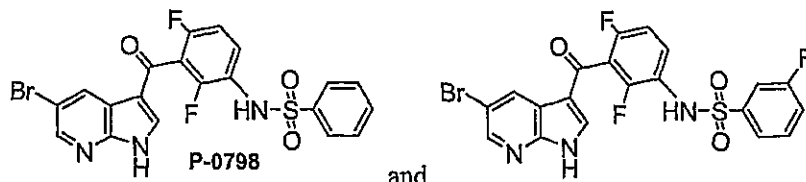
Step 4 – Preparation of 2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl chloride (46):

[0183] To 2,6-difluoro-3-(propane-1-sulfonylamino)-benzoic acid (45, 1.50 g, 5.4 mmol) was added toluene (7.0 mL) and thionyl chloride (15.0 mL, 0.21 mmol). The reaction was heated to reflux for 3 hours. The reaction was concentrated to give crude compound that was used in the next step.

Step 5- Preparation of propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (P-0773):

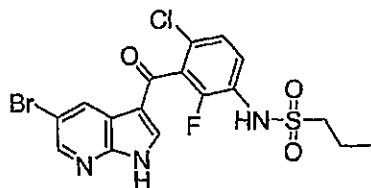
[0184] To aluminum trichloride (8.89 g, 66.7 mmol) was added methylene chloride (150 mL) under an atmosphere of nitrogen below 5 °C. Into this, 5-bromo-7-azaindole (67, 1.64 g, 8.34 mmol) in methylene chloride (20 mL) was added. The reaction was stirred for 60.0 minutes and 2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl chloride (46, 3.50 g, 11.8 mmol) in methylene chloride (20 mL) was added. The reaction was stirred for 6 hours and warmed to room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtrated and concentrated. The desired compound was isolated by silica gel column chromatography (methylene chloride/methanol 5%) to give a white solid (P-0773, 1.2 g, 31.4%). MS(ESI) $[M+H]^+ = 460.0, 462.0$.

[0185] N-[3-(5-Bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide **P-0798** and N-[3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-fluoro-benzenesulfonamide



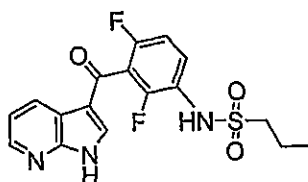
were prepared following the protocol of Scheme 13, substituting propane-1-sulfonyl chloride with benzenesulfonyl chloride and 3-fluoro-benzenesulfonyl chloride, respectively, in Step 2. **P-0798** MS(ESI) $[M - H^+] = 489.9, 491.9$.

[0186] Propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-chloro-2-fluoro-phenyl]-amide **P-0805**



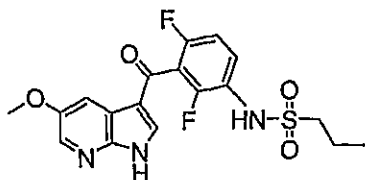
was prepared following the protocol of Scheme 13, substituting 2,4-difluoro-phenylamine with 4-chloro-2-fluoro-phenylamine in Step 1. MS(ESI) $[M - H^+] = 471.9, 473.9$.

[0187] Propane-1-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide **P-0007**



was prepared following the protocol of Scheme 13, substituting 5-bromo-7-azaindole with 7-azaindole in Step 5. MS(ESI) $[M + H^+]^+ = 380.1$.

[0188] Propane-1-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide **P-0806**

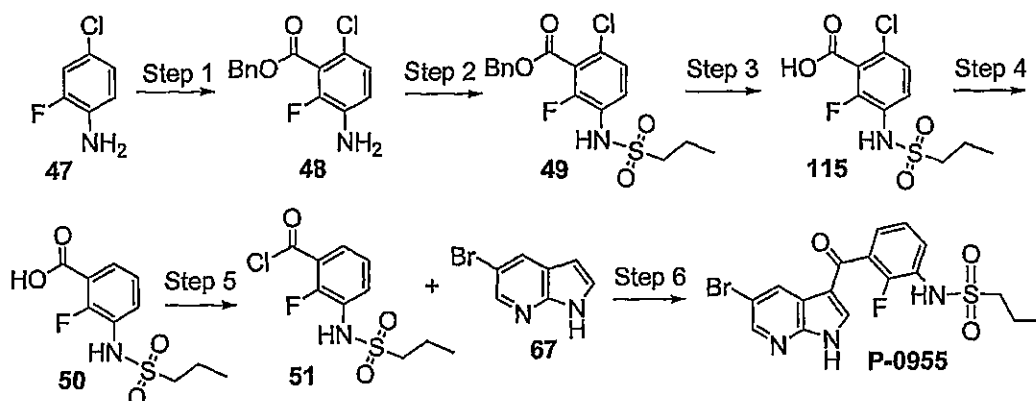


was prepared following the protocol of Scheme 13, substituting 5-bromo-7-azaindole with 5-methoxy-7-azaindole **104** (prepared as described in Example 16) in Step 5. MS(ESI) $[M - H]^+ = 410.1$.

Example 2: Synthesis of Propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide **P-0955 and related compounds.**

[0189] Compound **P-0955** was synthesized in six steps from 4-chloro-2-fluoro-phenylamine **47** as shown in Scheme 14.

Scheme 14



Step 1 – Preparation of 3-Amino-6-chloro-2-fluoro-benzoic acid benzyl ester (48):

[0190] To 4-chloro-2-fluoro-phenylamine (**47**, 6.30 mL, 57.0 mmol) in tetrahydrofuran (300 mL), cooled with dry ice/acetone bath under an atmosphere of nitrogen, was added *n*-butyllithium (2.500 M in hexane, 24.4 mL) slowly. After 20 minutes, 1,2-Bis-(chloro-dimethyl-silanyl)-ethane (12.9 g, 60.0 mmol) dissolved in tetrahydrofuran (40.0 mL) was added to the reaction slowly. After 1 hour, *n*-butyllithium (2.50 M in hexane, 25.0 mL) was added slowly to the reaction. The reaction was stirred at -78 °C for 20 minutes and allowed to warm to room temperature over 60 minutes. The reaction was cooled to -78 °C, followed by addition of *n*-butyllithium (2.50 M in hexane, 26.0 mL) slowly. After 80 minutes, benzyl chloroformate (10.0 mL, 70.0 mmol) was added to the reaction. The reaction mixture was stirred at -78 °C overnight followed by addition of water (80 mL) and concentrated hydrochloric acid (25 mL). The reaction was allowed to warm to room temperature for

2 hours. The organic layer was separated and the aqueous layer was basified with potassium carbonate and extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous sodium sulfate, filtrated and concentrated. The desired compound was isolated by silica gel column chromatography (ethyl acetate/hexane 20%) to give a colorless oil (48, 12.5 g, 78.3%). MS(ESI) $[M+H]^+ = 280.0$.

Step 2 – Preparation of 6-chloro-2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid benzyl ester (49):

[0191] To 3-amino-6-chloro-2-fluoro-benzoic acid benzyl ester (48, 1.20 g, 4.3 mmol) in methylene chloride (28 mL) was added pyridine (0.52 mL, 6.4 mmol) and propane-1-sulfonyl chloride (0.685 g, 4.8 mmol). The reaction was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated and concentrated. The desired compound was isolated with silica gel column chromatography to give a colorless oil (49, 960 mg, 58.0%). MS(ESI) $[M-H]^+ = 384.1$.

Step 3 – Preparation of 6-chloro-2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid (115):

[0192] To 6-chloro-2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid benzyl ester (49, 6.00 g, 15.6 mmol) in tetrahydrofuran (100 mL) was added 1.0 M aqueous potassium hydroxide (100 mL). The reaction was heated to reflux overnight. The reaction was poured into water, acidified to pH 2 with 1 N hydrochloric acid and extracted with ethyl acetate. The organic portion was dried over anhydrous sodium sulfate, filtrated and concentrated to give a white solid 115 (3.95 g, 85.8%).

Step 4 – Preparation of 2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid (50):

[0193] To 6-chloro-2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid (115, 0.69 g, 2.3 mmol) in methanol (10 mL) was added 20% palladium hydroxide on carbon (200 mg). The reaction was stirred under hydrogen at 50 psi for 2 hours. The reaction was filtrated and concentrated to give white solid 50 that was used in the next step. MS(ESI) $[M-H]^+ = 260.1$.

Step 5 – Preparation of 2-fluoro-3-(propane-1-sulfonylamino)-benzoyl chloride (51):

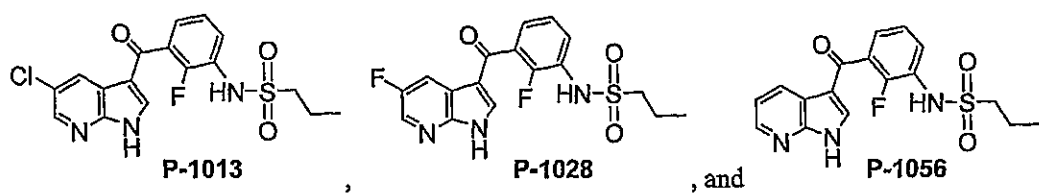
[0194] To 2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid (50, 1.17 g, 4.5 mmol) was added thionyl chloride (10.0 mL). The reaction was heated to reflux for 3 hours. The reaction was concentrated to give crude compound 51 that was used in the next step.

Step 6- Preparation of Propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide (P-0955):

[0195] Aluminum trichloride (2.52 g, 18.9 mmol) and methylene chloride (60.0 mL) were combined under an atmosphere of nitrogen. Into the reaction mixture, was added 5-bromo-7-azaindole (67, 630.0 mg, 3.2 mmol) in methylene dichloride (20.0 mL). The reaction was stirred at room

temperature for 70 minutes, then 2-fluoro-3-(propane-1-sulfonylamino)-benzoyl chloride (**51**, 0.749 g, 2.68 mmol) in methylene chloride (20 mL) was added. 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 30% ethyl acetate in hexane to give compound **P-0955** (65 mg, 5.5%). MS(ESI) $[M+H]^+ = 440.2, 442.2$.

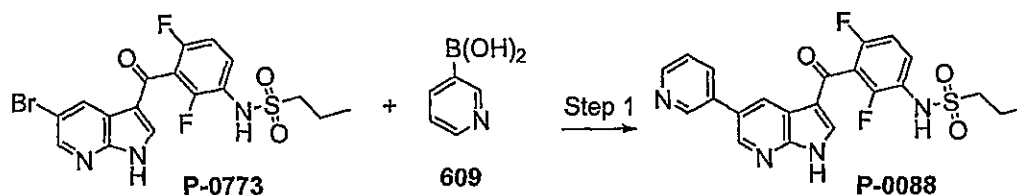
[0196] Using the protocol of Scheme 14, substituting 5-bromo-azaindole with either 5-chloro-7-azaindole (**80**, prepared as described in Example 9), 5-fluoro-7-azaindole (**81**, prepared as described in Example 9) or 7-azaindole in Step 6, propane-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide **P-1013** (MS(ESI) $[M - H]^- = 394.1$), propane-1-sulfonic acid [2-fluoro-3-(5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide **P-1028** (MS(ESI) $[M - H]^- = 378.1$), and propane-1-sulfonic acid [2-fluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide **P-1056** (MS(ESI) $[M + H]^+ = 362.2$) were prepared, respectively;



Example 3: Propane-1-sulfonic acid [2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide **P-0088 and related compounds.**

[0197] Compound **P-0088** was synthesized in one step from propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide **P-0773** by Suzuki coupling ((Muyaura and Suzuki, *Chem. Rev.* 1995, 95:2457) as shown in Scheme 15.

Scheme 15



*Step 1 – Preparation of propane-1-sulfonic acid [2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0088**):*

[0198] To propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0773**, prepared as described in Example 1, 65.0 mg, 0.14 mmol) in acetonitrile (4.0 mL) was added pyridine-3-boronic acid (**609**, 25.0 mg, 0.20 mmol), tetrakis

(triphenylphosphine)palladium(0) (11 mg, 1.0% mmol) and aqueous potassium carbonate (1.0 M, 2.0 mL). The reaction was heated to 160 °C for 10 minutes in a CEM Discover microwave instrument. The reaction was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated and concentrated. The desired compound was isolated by silica gel column chromatography (methylene chloride/methanol 5%) to give a white solid (**P-0088**, 30 mg, 46.9%). MS(ESI) $[M+H]^+ = 457.2$.

[0199] Additional compounds were prepared following the protocol of Scheme 15, optionally replacing propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide **P-0773** with an appropriate 5-bromo azaindole and/or pyridine-3-boronic acid **609** with an appropriate boronic acid or boronic acid ester. The 5-bromo azaindole used was synthesized as described in either Example 1, 2, 5, or 54. The following compounds were made following this procedure:

N-[2,4-Difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-0685**),

Propane-1-sulfonic acid [4-chloro-2-fluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0753**),

Propane-1-sulfonic acid [2,4-difluoro-3-(5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0636**),

Propane-1-sulfonic acid [4-chloro-2-fluoro-3-(5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0776**)

Propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (**P-0956**),

Propane-1-sulfonic acid {3-[5-(4-dimethylamino-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (**P-0889**),

Propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-0877**),

Propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-trifluoromethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-0912**),

Propane-1-sulfonic acid {2,4-difluoro-3-[5-(3-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-0874**),

Propane-1-sulfonic acid {3-[5-(3-dimethylamino-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (**P-0876**),

Propane-1-sulfonic acid [2-fluoro-3-(5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0897**),

Propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl}-amide (**P-1009**),

5-phenyl-1H-pyrrolo[2,3-b]pyridine,
Propane-1-sulfonic acid [2-fluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1251**),
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(3-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-1259**),
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-1260**),
Propane-1-sulfonic acid [2-fluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1261**),
Propane-1-sulfonic acid [2,4-difluoro-3-(5-pyridin-4-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1262**),
3-{3-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-benzoic acid (**P-1266**),
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(3-morpholin-4-yl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-1873**),
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(3-morpholin-4-ylmethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-1878**),
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(6-methoxy-pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-1879**),
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(6-morpholin-4-yl-pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-1881**),
Propane-1-sulfonic acid (2,4-difluoro-3-{5-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl}-phenyl)-amide (**P-1882**),
Propane-1-sulfonic acid {3-[5-(4-cyano-3,5-dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1980**),
N-{2,4-Difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-1996**),
N-{2,4-Difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-3-fluoro-benzenesulfonamide (**P-1997**),
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-1864**),
Propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-4-fluoro-phenyl}-amide (**P-1432**),
4-{3-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-benzamide (**P-1546**),
4-{3-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-N,N-dimethyl-benzamide (**P-1547**),

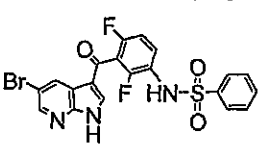
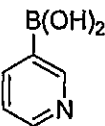
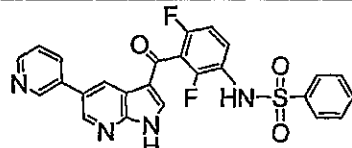
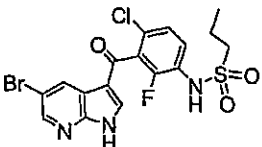
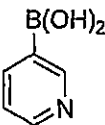
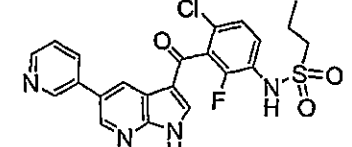
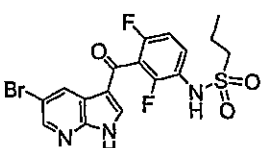
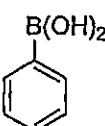
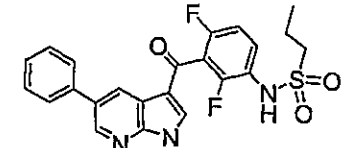
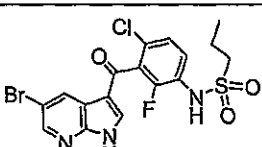
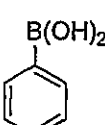
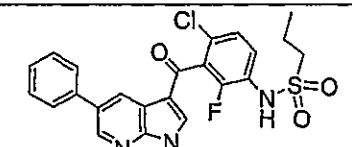
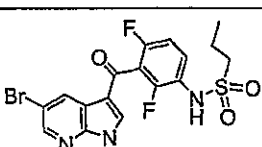
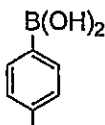
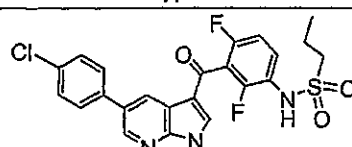
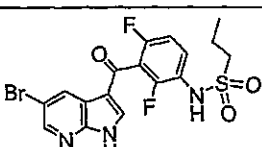
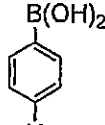
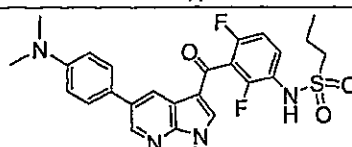
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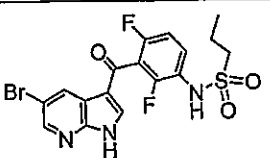
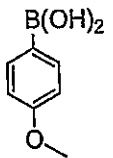
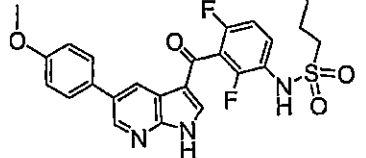
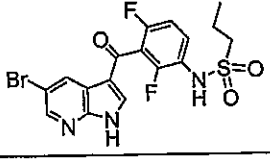
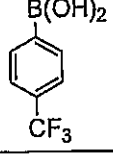
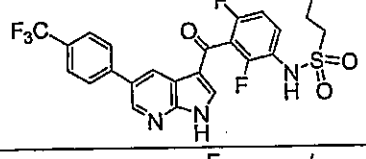
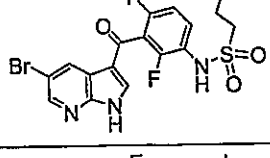
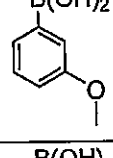
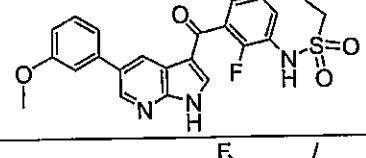
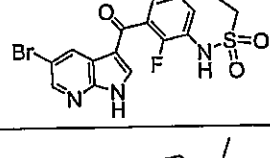
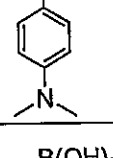
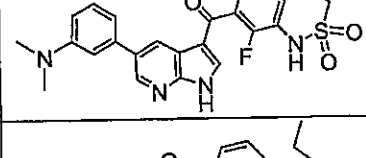
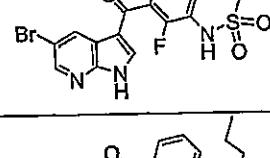
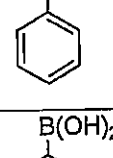
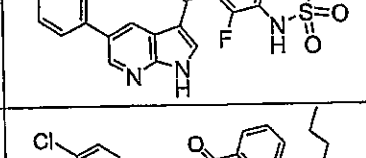
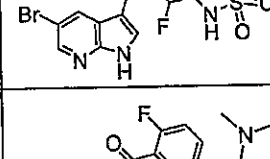
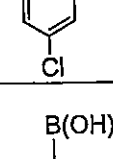
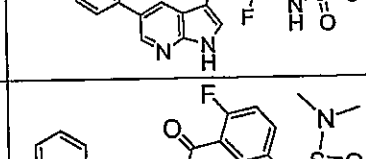
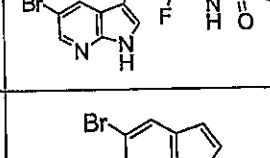
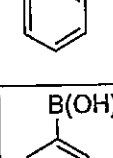
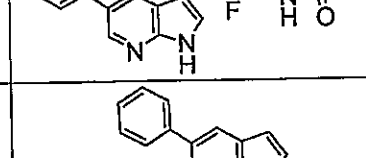
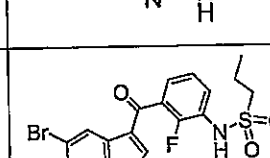
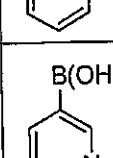
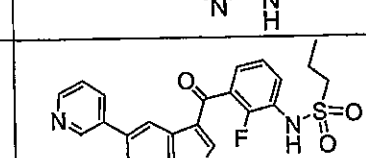
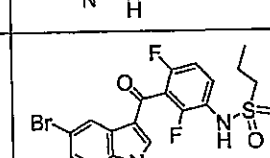
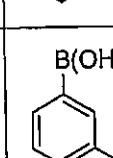
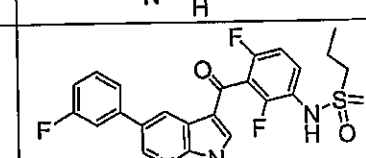
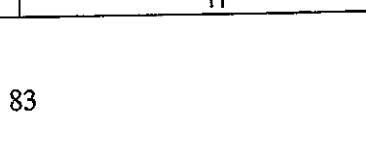
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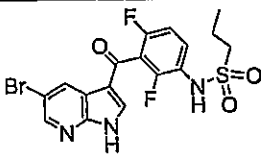
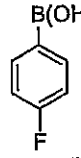
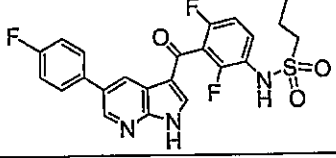
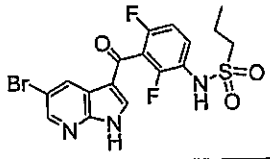
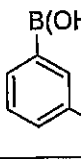
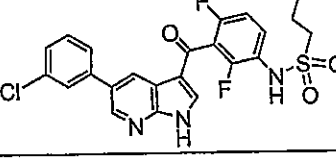
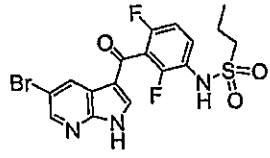
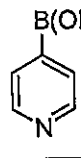
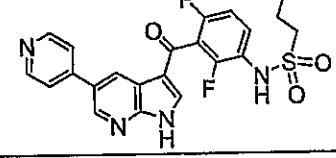
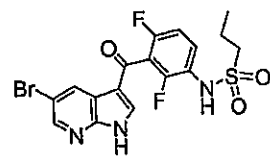
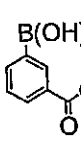
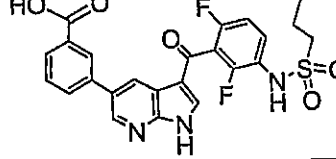
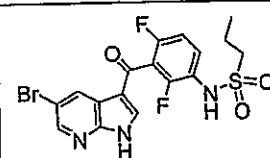
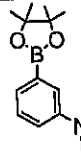
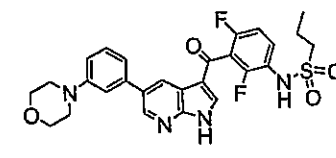
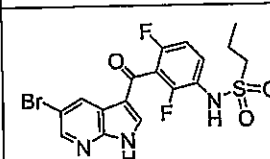
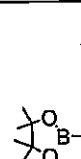
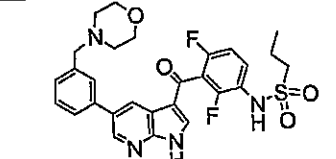
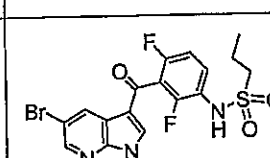
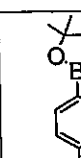
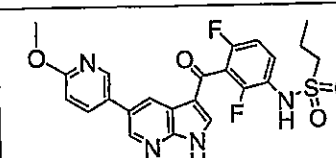
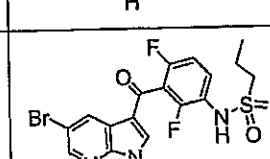
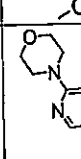
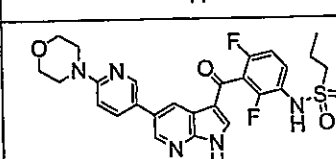
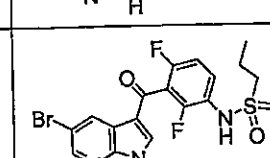
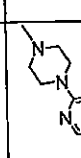
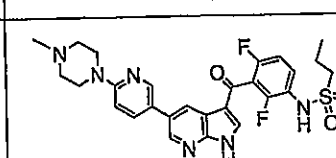
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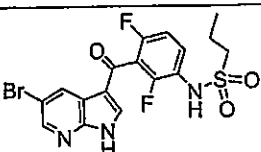
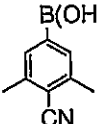
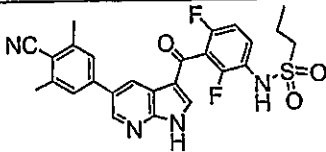
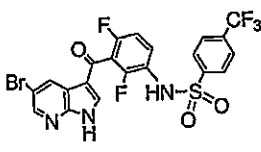
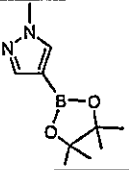
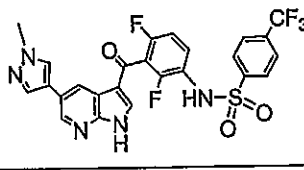
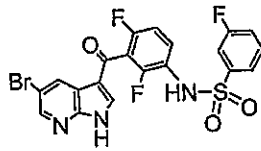
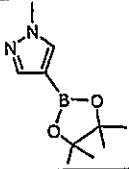
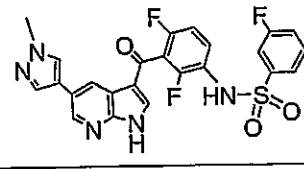
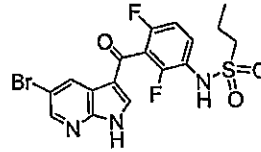
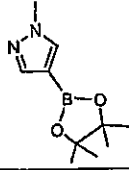
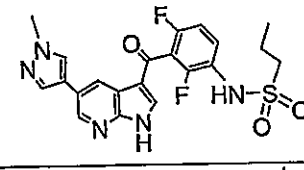
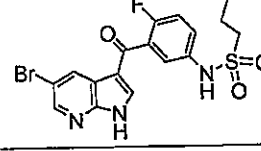
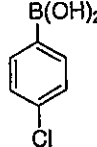
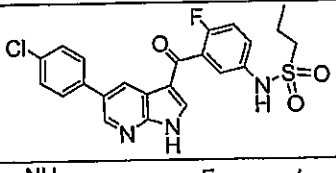
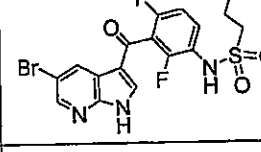
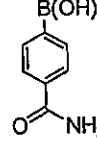
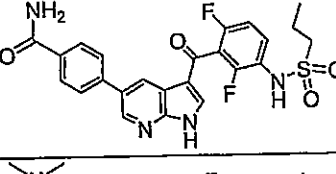
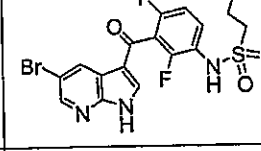
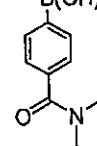
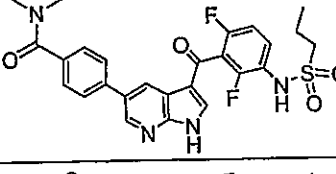
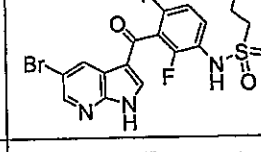
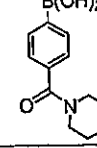
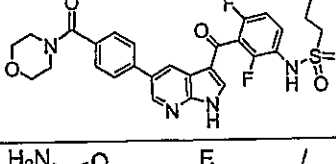
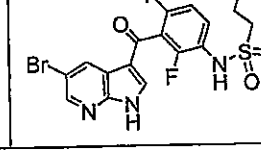
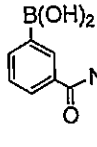
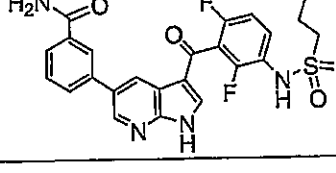
N-{2,4-Difluoro-3-[5-(6-methoxy-pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-3-fluoro-benzenesulfonamide (P-2012).

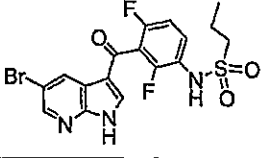
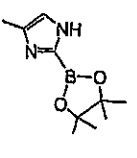
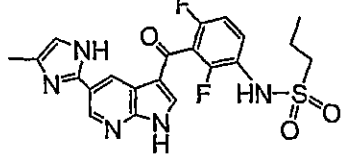
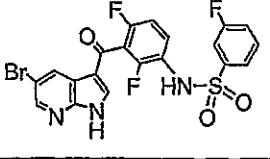
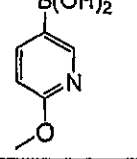
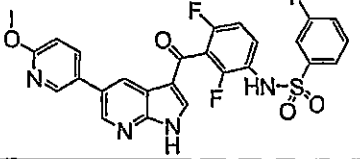
The following table indicates the 5-bromo azaindole (column 2) and boronic acid (column 3) used to afford the compound (column 4). Column 1 provides the compound number and column 5 the observed mass.

	5-Br azaindole	Boronic acid	Compound	MS(ESI) [M+H] ⁺ observed
P-0685				491.1
P-0753				473.1
P-0636				456.1
P-0776				472.1
P-0956				490.1
P-0889				499.2

	5-Br azaindole	Boronic acid	Compound	MS(ESI) [M+H] ⁺ observed
P-0877				486.3
P-0912				524.1
P-0874				484.3 [M-H] ⁺
P-0876				499.3
P-0897				438.3
P-1009				472.2
P-0857				455.1 [M-H] ⁺
				
P-1251				439.3
P-1259				474.2

	5-Br azaindole	Boronic acid	Compound	MS(ESI) [M+H] ⁺ observed
P-1260				474.2
P-1261				490.2
P-1262				457.2
P-1266				500.1
P-1873				541.2
P-1878				555.3
P-1879				487.3
P-1881				542.3
P-1882				555.3

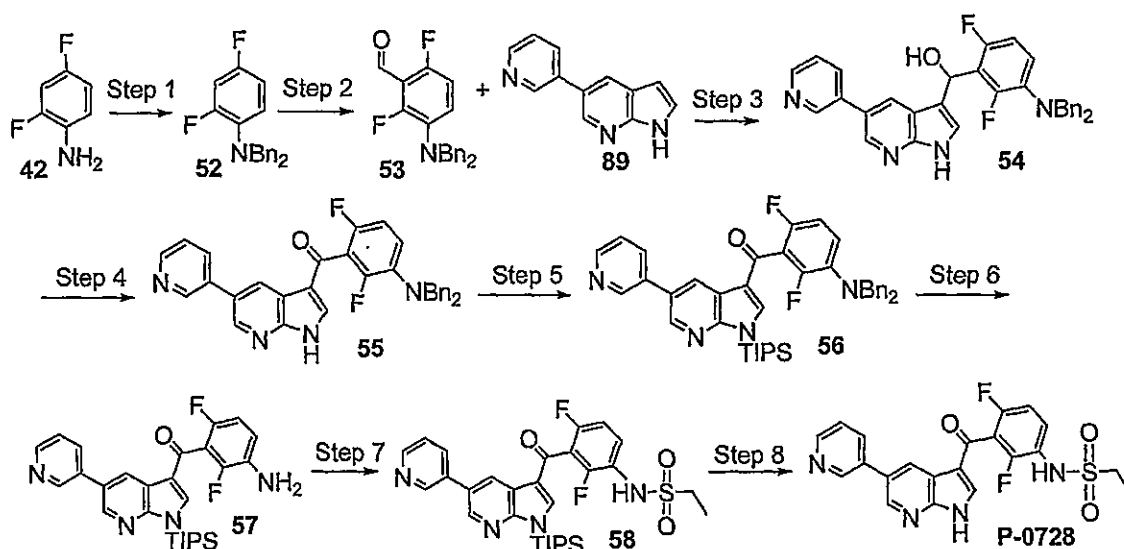
	5-Br azaindole	Boronic acid	Compound	MS(ESI) [M+H] ⁺ observed
P-1980				509.2
P-1996				562.2
P-1997				512.2
P-1864				460.2
P-1432				472.2
P-1546				497.2
P-1547				527.3
P-1548				569.3
P-1549				499.3

	5-Br azaindole	Boronic acid	Compound	MS(ESI) [M+H] ⁺ observed
P-2006				560.2
P-2012				632.1

Example 4: Synthesis of N-[2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-ethanesulfonamide P-0728.

[0200] Compound P-0728 was synthesized in eight steps from 2,4-difluorophenylamine 42 as shown in Scheme 16.

Scheme 16



Step 1 – Preparation of dibenzyl-(2,4-difluoro-phenyl)-amine (52):

[0201] To 2,4-difluoro-phenylamine (42, 10.0 g, 77.4 mmol) in N,N-dimethylformamide (130 mL) were added potassium carbonate (32.1 g, 0.23 mol) and benzyl bromide (21.2 mL, 0.18 mol). The reaction was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated and purified by silica gel column chromatography eluting

with 10% ethyl acetate in hexane. The appropriate fractions were combined and concentrated to provide the compound (**52**, 12.0 g, 50%). MS(ESI) $[M+H]^+ = 310.2$.

Step 2 – Preparation of 3-dibenzylamino-2,6-difluoro-benzaldehyde (53):

[0202] To dibenzyl-(2,4-difluoro-phenyl)-amine (**52**, 4.30 g, 13.9 mmol) in tetrahydrofuran (60 mL), under an atmosphere of nitrogen, cooled in a $-78\text{ }^{\circ}\text{C}$ acetone/dry ice bath, was added n-butyllithium (2.50 M in hexane, 6.1 mL, 15.3 mmol) slowly. The reaction was stirred for 1 hour, N,N-dimethylformamide (1.2 mL, 15.3 mmol) was added and the reaction was allowed to warm to room temperature for 1 hour. 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 provide the compound (**53**, 4.0 g, 85%). MS(ESI) $[M+H]^+ = 337.2$.

Step 3 – Preparation of (3-dibenzylamino-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (54):

[0203] To 3-dibenzylamino-2,6-difluoro-benzaldehyde (**53**, 0.76 g, 2.3 mmol) in methanol (50 mL) were added 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**89**, 0.40 g, 2.1 mmol, prepared as described in Example 17) and potassium hydroxide (0.50 g, 8.9 mmol) 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 washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 5% methanol in methylene chloride to provide the compound (**54**, 0.60 g, 50%). MS(ESI) $[M+H]^+ = 533.2$.

Step 4 – Preparation of (3-dibenzylamino-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (55):

[0204] To (3-dibenzylamino-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**54**, 0.90g, 1.7 mmol) in methylene chloride (20 mL) under an atmosphere of nitrogen was added Dess-Martin periodane (0.97 g, 2.3 mmol). The reaction was stirred at room temperature for 15 minutes. The reaction was poured into a solution of sodium bicarbonate and sodium thiosulfate 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 5% methanol in methylene chloride to provide the compound (**55**, 0.70 g, 78%). MS(ESI) $[M+H]^+ = 531.2$.

Step 5 – Preparation of (3-dibenzylamino-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (56):

[0205] To (3-dibenzylamino-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-

methanone (**55**, 0.84 g, 1.6 mmol) in tetrahydrofuran (150 mL) was added sodium hydride (210.0 mg, 60% in mineral oil, 5.3 mmol) under an atmosphere of nitrogen. The reaction was stirred for 5 minutes. Triisopropylsilyl chloride (0.80 mL, 3.8 mmol) was added and the reaction was stirred at room temperature for 3 hours. The reaction mixture 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 provide the compound (**56**, 420 mg, 39%). MS(ESI) $[M+H]^+ = 687.4$.

*Step 6 – Preparation of (3-amino-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**57**):*

[0206] To (3-dibenzylamino-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**56**, 55.0 mg, 0.080 mmol) in methanol (15 mL) was added 20% palladium hydroxide on carbon (20 mg). The reaction was stirred under an atmosphere of hydrogen overnight. The reaction was filtered to remove the catalyst, and then concentrated to give the crude compound that was used in the next step.

*Step 7 – Preparation of N-[2,4-difluoro-3-(5-pyridin-3-yl-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-ethanesulfonamide (**58**):*

[0207] To (3-amino-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**57**, 35.0 mg, 0.069 mmol) in methylene chloride (6 mL) was added methanesulfonyl chloride (0.30 mL, 3.9 mmol) and triethylamine (0.40 mL, 2.9 mmol). 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 concentrated to give the crude compound that was used in the next step.

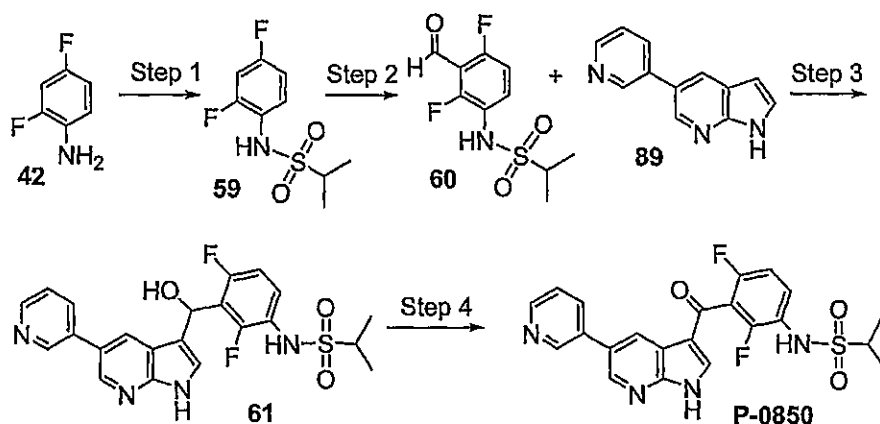
*Step 8 – Preparation of N-[2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-ethanesulfonamide (**P-0728**):*

[0208] To N-[2,4-difluoro-3-(5-pyridin-3-yl-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-ethanesulfonamide (**58**, 35.0 mg, 0.060 mmol) in tetrahydrofuran (10 mL) was added tetra-n-butylammonium fluoride (19 mg, 0.072 mmol). The reaction was stirred at room temperature for 5 minutes. 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 5% methanol in methylene chloride to provide the compound (**P-0728**, 5.6 mg, 22%). MS(ESI) $[M+H]^+ = 443.1$.

Example 5: Preparation of propane-2-sulfonic acid [2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide P-0850.

[0209] Compound P-0850 was synthesized in four steps from 2,4-difluorophenylamine 42 as shown in Scheme 17.

Scheme 17



Step 1 – Preparation of propane-2-sulfonic acid (2,4-difluoro-phenyl)-amide (59):

[0210] To 2,4-difluoro-phenylamine (42, 4.0 mL, 40.0 mmol) in methylene chloride (50 mL) were added pyridine (3.37 mL, 42.3 mmol), propane-2-sulfonyl chloride (6.00 g, 42.3 mmol) and dimethylaminopyridine (0.20 g, 1.64 mmol) under an atmosphere of nitrogen. The reaction was stirred at 45 °C overnight. 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 3% methanol in methylene chloride to give a white solid (59, 8.0 g, 85%). MS(ESI) $[M-H]^+$ = 234.0.

Step 2 – Preparation of propane-2-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (60):

[0211] To propane-2-sulfonic acid (2,4-difluoro-phenyl)-amide (59, 2.35 g, 9.95 mmol) in tetrahydrofuran (70 mL) under an atmosphere of nitrogen cooled with a dry ice/acetone bath was added 1.60 M of n-butyllithium (1.60 M in hexane, 6.53 mL, 10.45 mmol). The reaction was stirred for 40 minutes, and then another portion of n-butyllithium (1.60 M in hexane, 6.84 mL, 10.94 mmol). The reaction was stirred for 1 hour and N,N-dimethylformamide (0.92 mL, 11.9 mmol) was added. The reaction was allowed to warm to room temperature overnight. The reaction was poured into water extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated and purified by silica gel column chromatography (dichloromethane/methanol 5%) to give the compound (60, 1.4 g, 53.4%). MS(ESI) $[M-H]^+$ = 263.4.

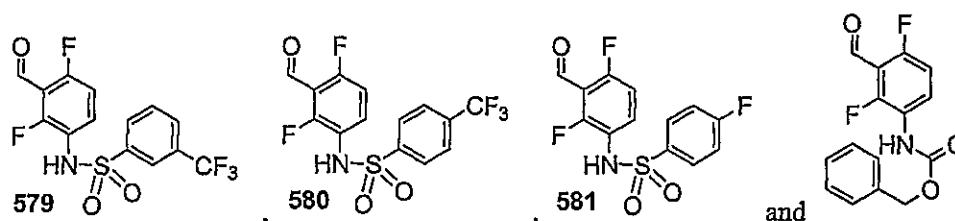
Step 3 – Preparation of propane-2-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (61):

[0212] To propane-2-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (**60**, 220.0 mg, 0.83 mmol) in methanol (15 mL) was added 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**89**, 150.0 mg, 0.77 mmol, prepared as described in Example 17) and potassium hydroxide (537.0 mg, 9.6 mmol) 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 washed with brine, dried over sodium sulfate and filtrated. The filtrate was concentrated and purified by silica gel column chromatography eluting with 5% methanol in dichloromethane to give the compound (**61**, 160 mg, 45.3%). In this step, minor compound Propane-2-sulfonic acid {2,4-difluoro-3-[methoxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide was also formed and isolated. MS(ESI) $[M + H]^+ = 460.1$.

Step 4 – Preparation of propane-2-sulfonic acid [2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (P-0850):

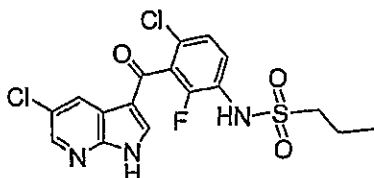
[0213] To propane-2-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**61**, 40.0 mg, 0.087 mmol) in tetrahydrofuran (10 mL) was added Dess-Martin periodane (48.0 mg, 0.11 mmol). The reaction was stirred at room temperature for 5 minutes. The reaction was poured into sodium thiosulfate and potassium carbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated and purified by silica gel column chromatography eluting with 5% methanol in methylene chloride to give the compound (**P-0850**, 13.4 mg, 33.5%). MS(ESI) $[M + H]^+ = 458.1$.

[0214] N-(2,4-Difluoro-3-formyl-phenyl)-3-trifluoromethyl-benzenesulfonamide **579**, N-(2,4-difluoro-3-formyl-phenyl)-4-trifluoromethyl-benzenesulfonamide **580**, and N-(2,4-difluoro-3-formyl-phenyl)-4-fluoro-benzenesulfonamide **581**, and (2,4-difluoro-3-formyl-phenyl)-carbamic acid benzyl ester



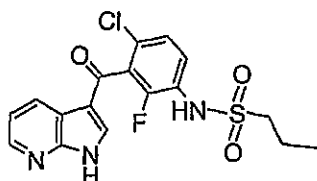
were prepared following Steps 1 and 2 of Scheme 17, substituting propane-2-sulfonyl chloride with 3-trifluoromethyl-benzenesulfonyl chloride, 4-trifluoromethyl-benzenesulfonyl chloride, 4-fluoro-benzenesulfonyl chloride, and benzyl chloroformate, respectively, in Step 1.

[0215] Propane-1-sulfonic acid [4-chloro-3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide **P-1004**



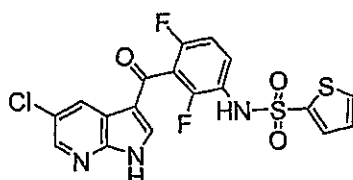
was prepared using the protocol of Scheme 17, substituting 2,4-difluoro-phenylamine with 4-chloro-2-fluoro-phenylamine and propane-2-sulfonyl chloride with propane-1-sulfonyl chloride in Step 1, and 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** with 5-chloro-7-azaindole **80** (see Example 9) in Step 3. MS(ESI) $[M + H]^+ = 430.1$.

[0216] Propane-1-sulfonic acid [4-chloro-2-fluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide **P-0904**



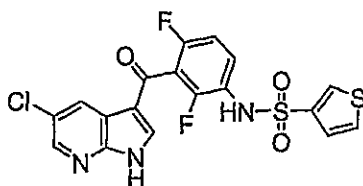
was prepared using the protocol of Scheme 17, substituting 2,4-difluoro-phenylamine with 4-chloro-2-fluoro-phenylamine and propane-2-sulfonyl chloride with propane-1-sulfonyl chloride in Step 1, and 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** with 7-azaindole **94** in Step 3. MS(ESI) $[M + H]^+ = 396.2$.

[0217] Thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide **P-1267**



was prepared using the protocol of Steps 3 and 4 of Scheme 17, substituting 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** with 5-chloro-7-azaindole **80** (see Example 9) and propane-2-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **60** with thiophene-2-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **512** (see Example 21) in Step 3. MS(ESI) $[M + H]^+ = 451.9$.

[0218] Thiophene-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide **P-1268**



was prepared using the protocol of Steps 3 and 4 of Scheme 17, substituting 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** with 5-chloro-7-azaindole **80** (see Example 9) and propane-2-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **60** with thiophene-3-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **513** (see Example 21) in Step 3. MS(ESI) $[M + H]^+ = 454.1$.

[0219] Additional compounds were prepared following the protocol of Scheme 17, optionally replacing propane-2-sulfonyl chloride with an appropriate acid chloride in Step 1 and/or 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine with an appropriate azaindole in Step 3. Azaindoles were purchased or synthesized as described in Examples 6, 13, 14, 16 and 17. Some compounds were isolated after Step 3, as either hydroxy or methoxy derivatives. The following compounds were made following this procedure:

Dimethylamine-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1257**),

N-[3-(5-Bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide (**P-0798**),

Propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0773**),

Dimethylamine-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0898**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide (**P-0885**),

N-[2,4-Difluoro-3-(5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-0902**),

Propane-1-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-isopropenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**P-1239**),

Propane-1-sulfonic acid [2,4-difluoro-3-(5-isopropenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0991**),

Propane-1-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**P-1240**),

Propane-1-sulfonic acid {2,4-difluoro-3-[methoxy-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**P-1241**),

Propane-1-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-isopropyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**P-1242**),

Propane-1-sulfonic acid [2,4-difluoro-3-(5-isopropyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0997**),

Propane-1-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**P-1243**),

Propane-1-sulfonic acid {2,4-difluoro-3-[methoxy-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**P-1244**),

Propane-1-sulfonic acid (2,4-difluoro-3-{hydroxy-[5-(4-methyl-piperazin-1-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methyl}-phenyl)-amide (**P-1245**),

Propane-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0933**),

Propane-1-sulfonic acid [2,4-difluoro-3-(5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0907**),

Piperidine-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1020**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-methoxy-benzenesulfonamide (**P-0983**),

N-[3-(4-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide (**P-0954**),

Dimethylamine-1-sulfonic acid [3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0950**),

Dimethylamine-1-sulfonic acid [3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0837**),

Dimethylamine-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1258**),

Butane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1263**),

Butane-1-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1264**),

Butane-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1265**),

Propane-1-sulfonic acid [3-(5-ethoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1252**),

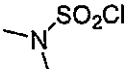
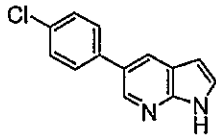
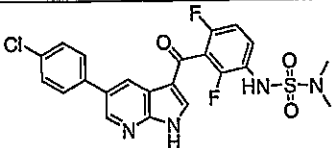
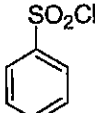
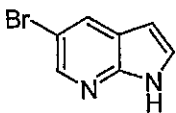
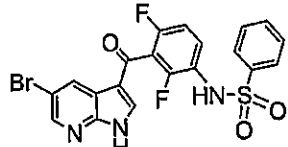
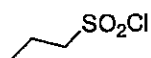
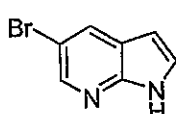
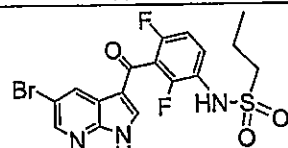
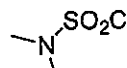
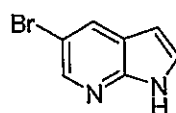
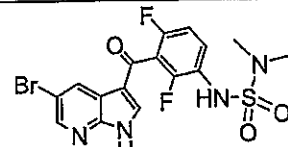
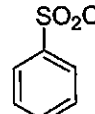
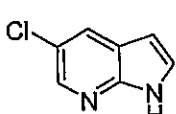
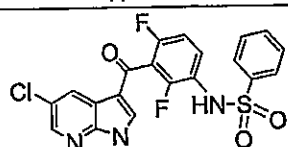
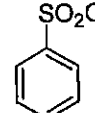
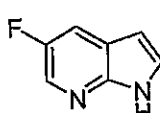
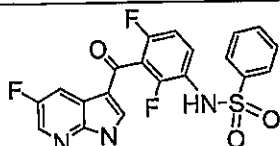
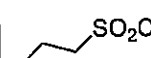
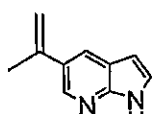
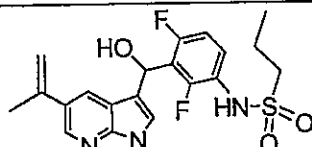
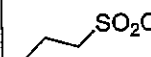
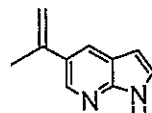
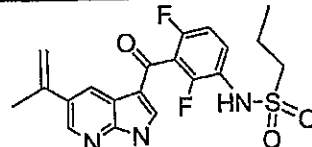
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide (**P-1253**),

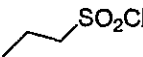
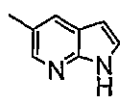
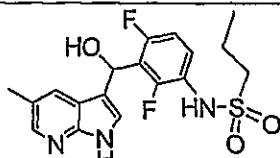
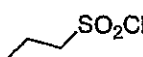
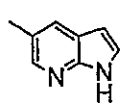
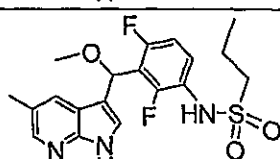
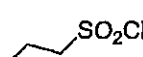
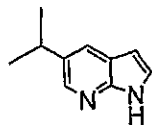
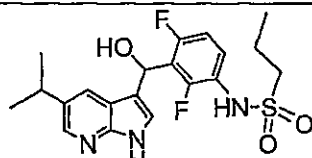
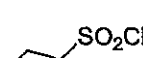
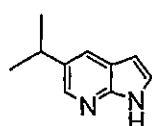
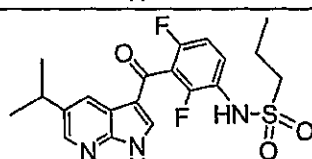
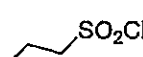
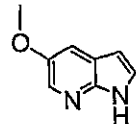
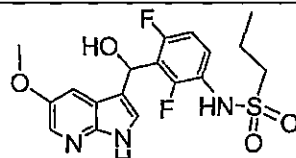
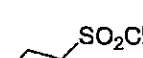
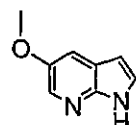
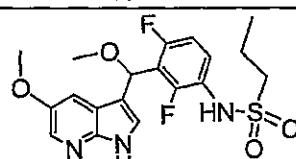
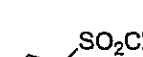
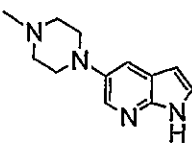
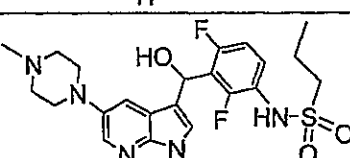
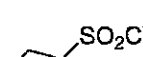
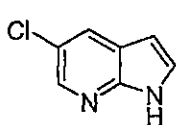
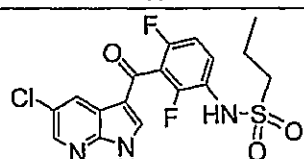
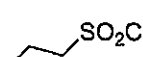
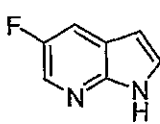
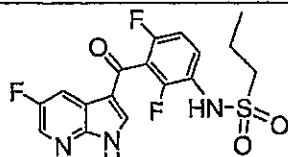
Propane-1-sulfonic acid {3-[5-(2-diethylamino-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (**P-1254**),

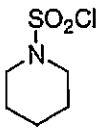
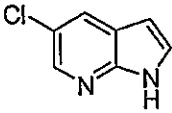
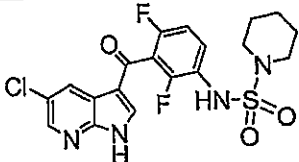
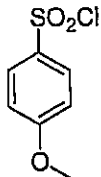
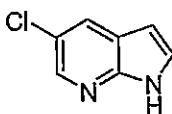
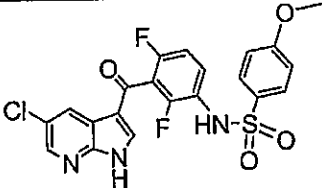
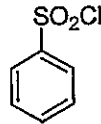
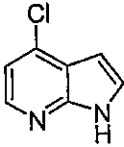
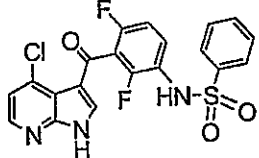
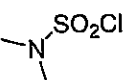
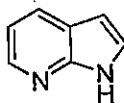
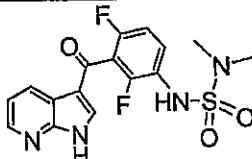
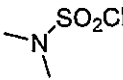
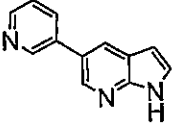
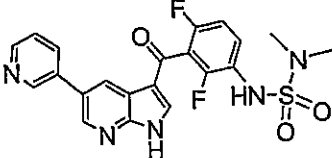
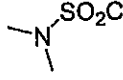
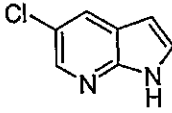
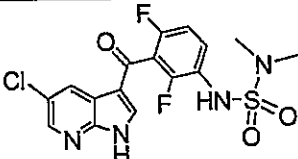
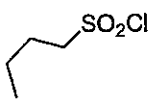
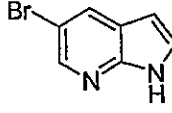
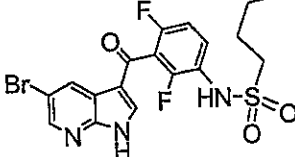
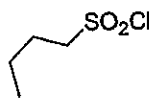
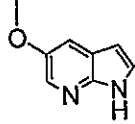
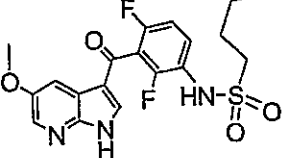
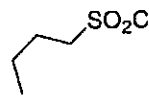
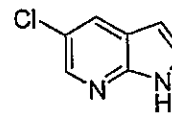
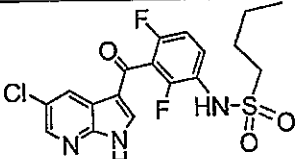
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-ethyl-

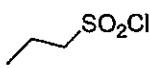
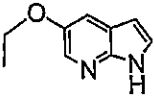
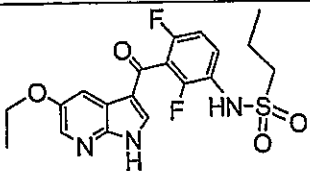
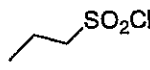
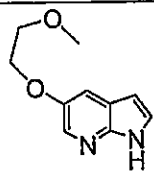
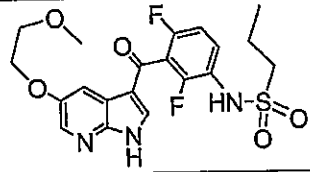
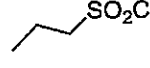
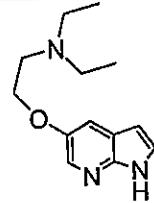
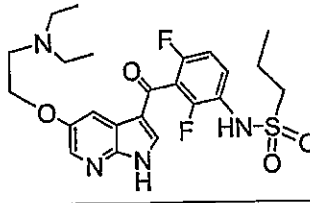
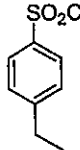
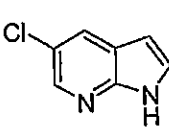
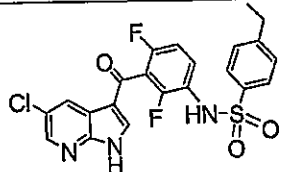
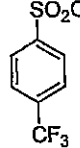
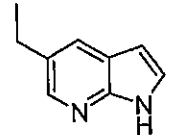
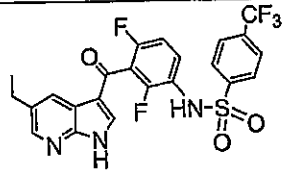
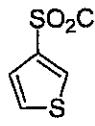
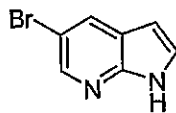
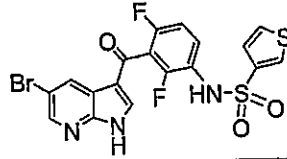
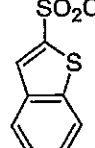
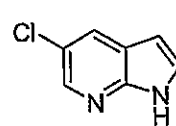
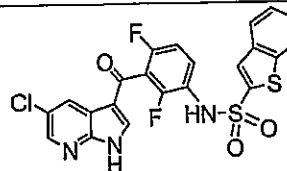
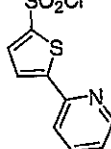
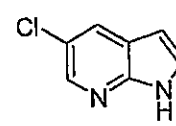
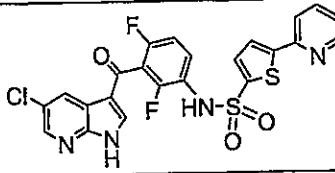
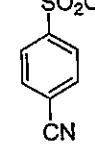
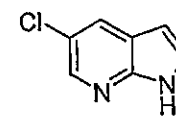
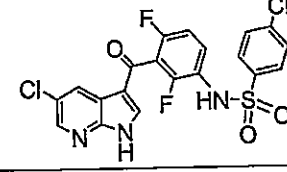
benzenesulfonamide (**P-1700**),
N-[3-(5-Ethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1783**),
Thiophene-3-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1798**),
Benzo[b]thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1799**),
5-Pyridin-2-yl-thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1800**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-cyano-benzenesulfonamide (**P-1822**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-fluoro-4-methyl-benzenesulfonamide (**P-1823**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-isopropyl-benzenesulfonamide (**P-1839**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-fluoro-benzenesulfonamide (**P-1840**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3,5-difluoro-benzenesulfonamide (**P-1841**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-methyl-benzenesulfonamide (**P-1842**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-oxazol-5-yl-benzenesulfonamide (**P-1843**),
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-fluoro-benzenesulfonamide (**P-1865**),
N-{2,4-Difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-3-fluoro-benzenesulfonamide (**P-1871**),
N-{2,4-Difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-fluoro-benzenesulfonamide (**P-1872**),
Propane-1-sulfonic acid (2,4-difluoro-3-{5-[4-(2-methoxy-ethoxy)-phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl}-phenyl)-amide (**P-1998**),
N-{2,4-Difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-2005**), and
N-(2,4-Difluoro-3-{5-[4-(2-methoxy-ethoxy)-phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl}-phenyl)-4-trifluoromethyl-benzenesulfonamide (**P-2013**).

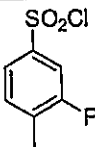
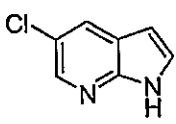
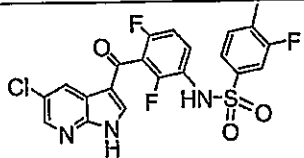
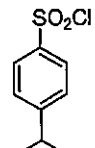
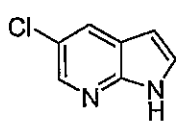
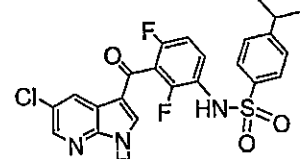
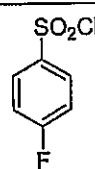
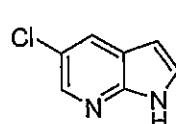
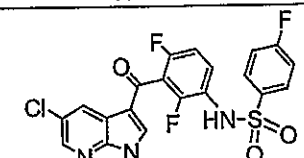
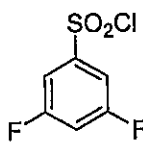
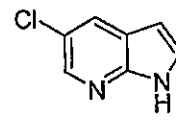
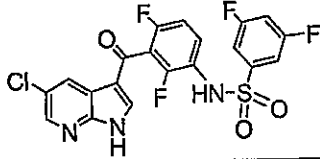
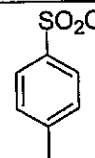
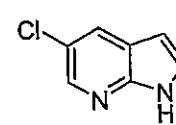
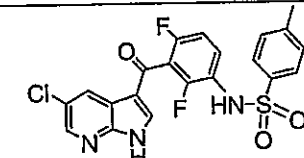
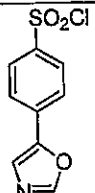
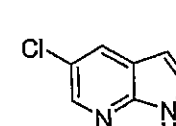
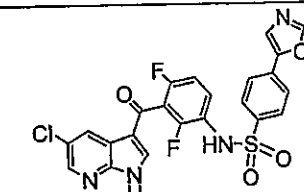
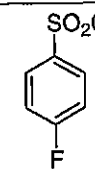
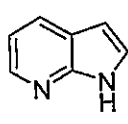
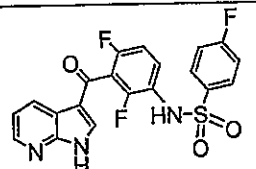
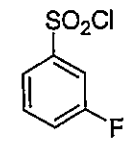
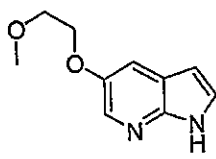
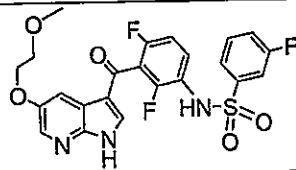
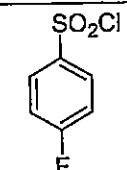
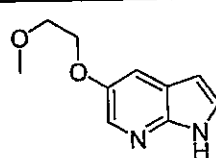
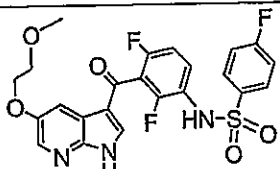
The following table indicates the acid chloride (column 2) and the azaindole (column 3) used to afford the target compounds (column 4). Column 1 provides the compound number and column 5 the observed mass. Compounds isolated after Step 3 of Scheme 17 are so noted in column 1.

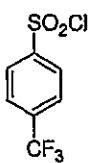
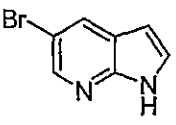
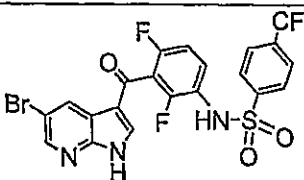
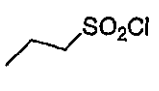
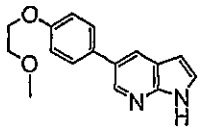
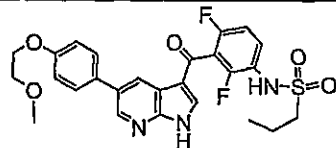
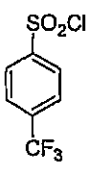
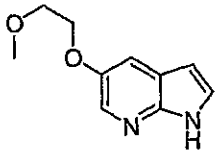
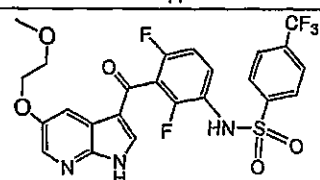
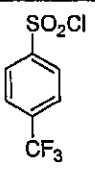
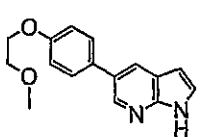
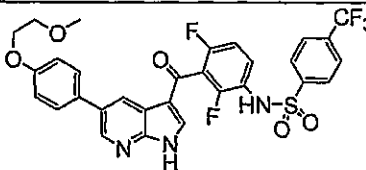
	Sulfonyl chloride	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1257				415.1
P-0798				489.9 491.1 [M-H] ⁺
P-0773				455.9 457.9 [M-H] ⁺
P-0898				497.0 499.1
P-0885				446.1 448.1 [M-H] ⁺
P-0902				430.1 [M-H] ⁺
P-1239 Step 3				422.2 [M-H] ⁺
P-0991				420.2

	Sulfonyl chloride	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1240 Step 3				396.4 [M-H] ⁺
P-1241 Step 3				410.3 [M-H] ⁺
P-1242 Step 3				424.3 [M-H] ⁺
P-0997				422.3
P-1243 Step 3				412.3 [M-H] ⁺
P-1244 Step 3				426.4 [M-H] ⁺
P-1245 Step 3				480.3 [M-H] ⁺
P-0933				414.2
P-0907				396.1 [M-H] ⁺

	Sulfonyl chloride	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1020				455.2
P-0983				476.1 [M-H] ⁻
P-0954				448.2
P-0950				381.2
P-0837				458.1
P-1258				415.1
P-1263				472.1 474.1
P-1264				424.2
P-1265				426.0 [M-H] ⁺

	Sulfonyl chloride	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1252				424.2
P-1253				454.2
P-1254				495.3
P-1700				476.2
P-1783				510
P-1798				495.9 497.6 [M-H] ⁺
P-1799				502.0 (-)
P-1800				531.1
P-1822				473.1

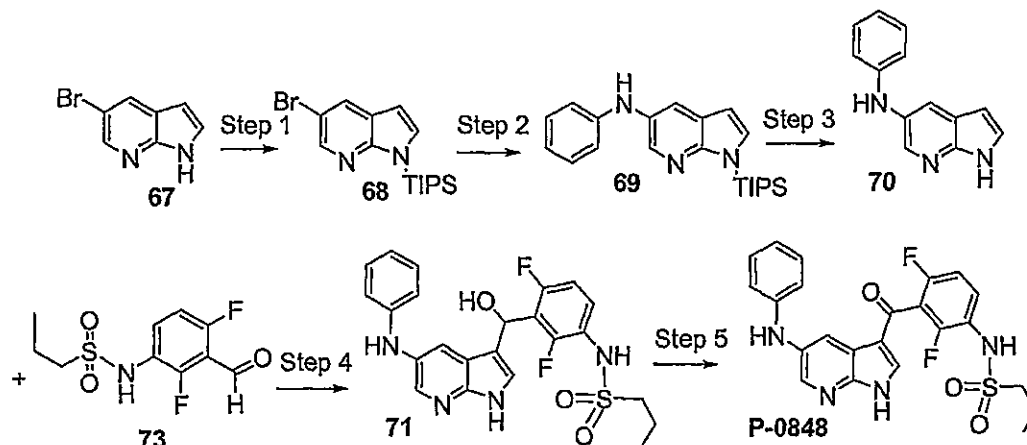
	Sulfonyl chloride	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1823				480.1
P-1839				488
P-1840				464
P-1841				482
P-1842				460.0 [M-H] ⁺
P-1843				513.0 [M-H] ⁺
P-1865				432.1
P-1871				506.2
P-1872				506.2

	Sulfonyl chloride	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
				
P-1998				530.3
P-2005				556.0
P-2013				539.2

Example 6: Synthesis of propane-1-sulfonic acid [2,4-difluoro-3-(5-phenylamino-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide P-0848 and related compounds.

[0220] Propane-1-sulfonic acid [2,4-difluoro-3-(5-phenylamino-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide **P-0848** was synthesized in five steps from 5-bromo-7-azaindole **67** as shown in Scheme 18.

Scheme 18



Step 1 - Preparation of 5-bromo-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (68):

[0221] To 5-bromo-7-azaindole (67, 1.5 g, 7.6 mmol) in N,N-dimethylformamide (20 mL) were added sodium hydride (60% in mineral oil, 0.27 g, 11.0 mmol) and triisopropylsilyl chloride (2.6 mL, 12.0 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 the compound (68, 1.6 g, 59%). MS(ESI)[M+H]⁺ = 352.3.

Step 2 - Preparation of 5-phenyl-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-5-yl)-amine (69):

[0222] To 5-bromo-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (68, 0.10 g, 0.3 mmol) in toluene (5 mL) were added aniline (0.04 mL, 0.42 mmol), sodium *tert*-butoxide (0.15 g, 1.56 mmol), tris(dibenzylideneacetone)dipalladium(0) (9.2 mg, 0.01 mmol) and (S) -(S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (6.3 mg, 0.01 mmol). The reaction was heated to 160 °C for 10 minutes in a CEM Discover microwave instrument. The reaction was concentrated and purified by silica gel column chromatography eluting with 3 % ethyl acetate in hexane to give the compound (69, 40 mg, 40%). MS(ESI)[M+H]⁺ = 366.6.

Step 3 - Preparation of phenyl-(1H-pyrrolo[2,3-b]pyridine-5-yl)-amine (70):

[0223] To 5-phenyl-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-5-yl)-amine (69, 0.14 g, mmol) in tetrahydrofuran (3.0 mL) was added tetra-n-butylammonium fluoride (0.197 g, 0.76 mmol). The reaction was stirred for 1 hour at room temperature. The reaction was concentrated and purified by silica gel column chromatography eluting with 3 % ethyl acetate in hexane to give the compound (70, 60 mg, 76 %). MS(ESI)[M+H]⁺ = 210.3.

Step 4 - Preparation of propane-1-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-phenylamino-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (71):

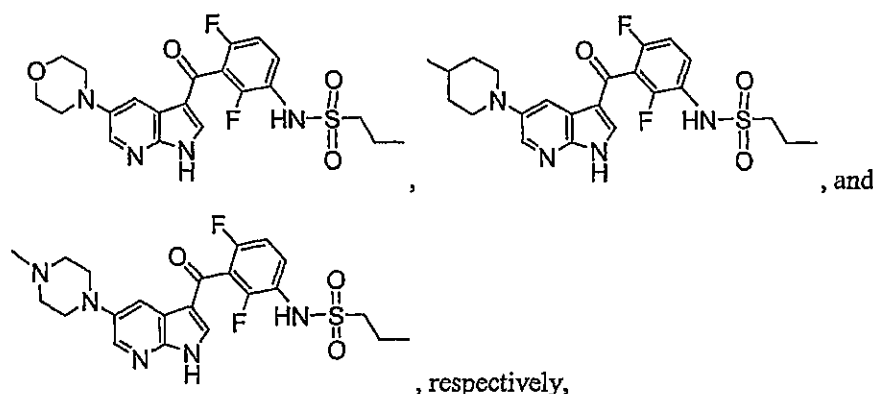
[0224] To phenyl-(1H-pyrrolo[2,3-b]pyridine-5-yl)-amine (70, 17.0 mg, 0.09 mmol) in methanol (5.0 mL) were added potassium hydroxide (92.0 mg, 1.6 mmol) and propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (73, 19.0 mg, 0.072 mmol, prepared as described in Example 7) under an atmosphere of nitrogen. The reaction was stirred for 12 hours at room temperature. The reaction was concentrated and purified by silica gel column chromatography eluting with 1 % methanol in dichloromethane to give the compound (71, 17 mg, 50%). MS(ESI)[M+H]⁺ = 473.5.

Step 5 - Preparation of propane-1-sulfonic acid [2,4-difluoro-3-(5-phenylamino-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (P-0848):

[0225] To propane-1-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-phenylamino-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (71, 7.5 mg, 0.016 mmol) in tetrahydrofuran (3 mL) was

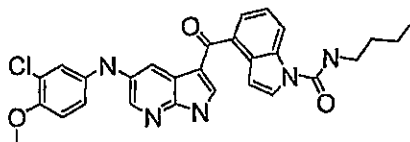
added Dess-Martin periodane (6.70 mg, 0.0158 mmol) under an atmosphere of nitrogen. The reaction was stirred for 20 minutes. The reaction was concentrated and purified by silica gel column chromatography eluting with 1 % methanol in dichloromethane to give the compound (**P-0848**, 6.2 mg, 84%). MS(ESI)[M+H]⁺ = 471.2.

[0226] Propane-1-sulfonic acid [2,4-difluoro-3-(5-morpholin-4-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide **P-0853**, propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-methyl-piperidin-1-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide **P-0860**, and propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-methyl-piperazin-1-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide **P-1246**,



were prepared using the protocol of Scheme 18, substituting aniline with morpholine, 4-methyl-piperidine, and 4-methyl-piperazine, respectively, in Step 2. **P-0853** MS(ESI) [M + H]⁺ = 465.2. **P-0860** MS(ESI) [M + H]⁺ = 477.3. **P-1246** MS(ESI) [M - H]⁺ = 478.4.

[0227] 4-[5-(3-Chloro-4-methoxy-phenylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-indole-1-carboxylic acid butylamide **P-1859**

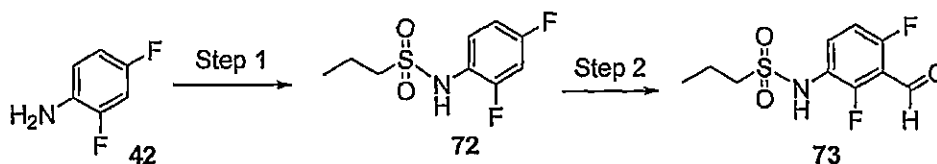


was prepared using the protocol of Scheme 18, substituting aniline with 3-chloro-4-methoxy-phenylamine in Step 2 and propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **73** with 4-Formyl-indole-1-carboxylic acid butylamide **519** (see Example 22) in Step 4. MS(ESI) [M + H]⁺ = 516.2.

Example 7: Synthesis of propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **73**.

[0228] Compound **73** was synthesized in two steps from 2,4-difluorophenylamine **42** as shown in Scheme 19.

Scheme 19



Step 1 - Preparation of Propane-1-sulfonic acid (2,4-difluoro-phenyl)-amide (72):

[0229] To 2,4-difluoro-phenylamine (42, 3.0 mL, 29.8 mmol) in tetrahydrofuran (50 mL) were added triethylamine (9.13 mL, 65.5 mmol) and propane-1-sulfonyl chloride (2.90 mL, 25.8 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight. The reaction was poured into 1 M HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give the compound (72, 2.0 g, 28%) that was used in the next step.

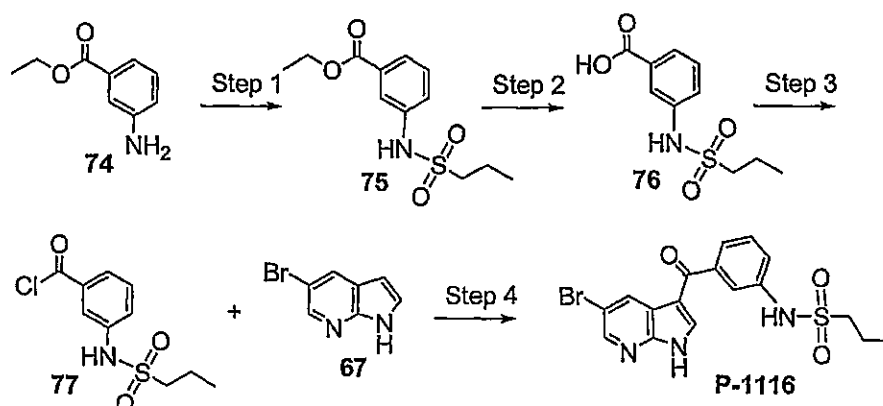
Step 2 - Preparation of propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (73):

[0230] To propane-1-sulfonic acid (2,4-difluoro-phenyl)-amide (72, 1.5 g, 6.38 mmol) in tetrahydrofuran (10 mL) under an atmosphere of nitrogen, cooled in a -78 °C acetone/dry ice bath was added lithium diisopropylamide (0.80 M in tetrahydrofuran, 24 mL, freshly prepared from n-butyllithium and diisopropylamine). After 30 minutes, N,N-dimethyl-formamide (542 µL, 7.018 mmol) was added dropwise to the reaction. The reaction was stirred for 30 minutes at -78 °C and then allowed to warm to room temperature for 40 minutes. 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 5 % ethyl acetate in hexane to give a light yellow solid (73, 300 mg, 18 %). MS(ESI)[M-H⁺] = 262.3.

Example 8: Synthesis of propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide P-1116.

[0231] Compound P-1116 was synthesized in four steps from 3-amino-benzoic acid ethyl ester 74 as shown in Scheme 20.

Scheme 20



Step 1 – Preparation of 3-(propane-1-sulfonylamino)-benzoic acid ethyl ester (75):

[0232] To 3-amino-benzoic acid ethyl ester (74, 5.0 g, 0.030 mol) in methylene chloride (30.0 mL) were added pyridine (3.67 mL, 0.045 mol) and propane-1-sulfonyl chloride (3.75 mL, 33.0 mmol). The reaction was stirred at room temperature for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The desired compound was isolated by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a white solid (75, 6.0 g, 74.1%).

Step 2 – Preparation of 3-(propane-1-sulfonylamino)-benzoic acid (76):

[0233] To 3-(propane-1-sulfonylamino)-benzoic acid ethyl ester (75, 1.60 g, 5.90 mmol) in water was added lithium hydroxide (1.0 g, 4.2 mmol) and tetrahydrofuran (20 mL). The reaction was stirred at room temperature overnight. The reaction mixture was acidified with 1 N HCl, 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 the compound (76, 1.2 g, 84.5%) as white solid. MS(ESI)[M-H]⁺ = 242.1.

Step 3 – Preparation of 3-(propane-1-sulfonylamino)-benzoyl chloride (77):

[0234] A solution of 3-(propane-1-sulfonylamino)-benzoic acid (76, 1.20 g, 4.93 mmol) in thionyl chloride was heated to reflux for 3.0 hours. Evaporation of the solvent gave compound 77 as white solid that was used for the next step.

Step 4 – Preparation of propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (P-1116):

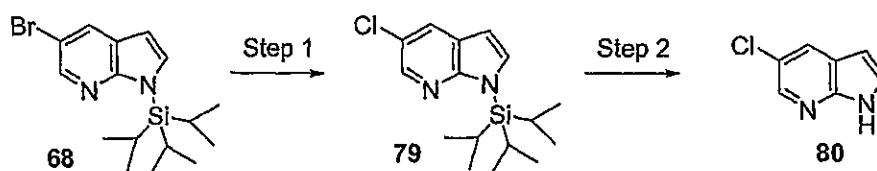
[0235] To aluminum trichloride (4.8 g, 36.0 mmol) in methylene chloride (70.0 mL), under an atmosphere of nitrogen, was added 5-bromo-1H-pyrrolo[2,3-b]pyridine (67, 797 mg, 4.04 mmol) dissolved in methylene chloride (5.0 mL). The reaction was stirred at room temperature for 30 minutes, followed by addition of 3-(propane-1-sulfonylamino)-benzoyl chloride (77, 1.10 g, 4.20

mmol) dissolved in methylene dichloride (4.0 mL). 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 30% ethyl acetate in hexane to give a white solid (P-1116, 300.0 mg). MS(ESI)[M-H]⁺ = 420.1, 422.1.

Example 9: Synthesis of 5-chloro-1H-pyrrolo[2,3-b]pyridine 80.

[0236] Compound 80 was synthesized in two steps from 5-bromo-1-triisopropylsilyl-7-azaindole 68 as shown in Scheme 21.

Scheme 21



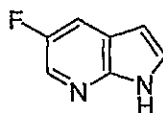
Step 1 – Preparation 5-chloro-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (79):

[0237] To 5-bromo-1-triisopropylsilyl-7-azaindole (68, 1.60 g, 4.53 mmol, prepared as described in Example 6) in tetrahydrofuran (50.0 mL), under an atmosphere of nitrogen at -78 °C, was added *tert*-butyllithium (1.70 M in hexane, 6.12 mL). The reaction was stirred for 1 hour, followed by addition of hexachloroethane (1.29 g, 5.43 mmol). The reaction was stirred for 3 hours, 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 the crude compound (79, 1.60 g). MS(ESI)[M+H]⁺ = 309.3.

Step 2 – Preparation 5-chloro-1H-pyrrolo[2,3-b]pyridine (80):

[0238] To 5-chloro-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (79, 1.40 g, 4.53 mmol) in tetrahydrofuran (15 mL) was added *tetra*-n-butylammonium fluoride (1.42 g, 5.43 mmol). The reaction mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated and isolated by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give the compound (80, 0.40 g, 58% over 2 steps). MS(ESI)[M-H]⁺ = 153.1.

[0239] 5-Fluoro-1H-pyrrolo[2,3-b]pyridine 81

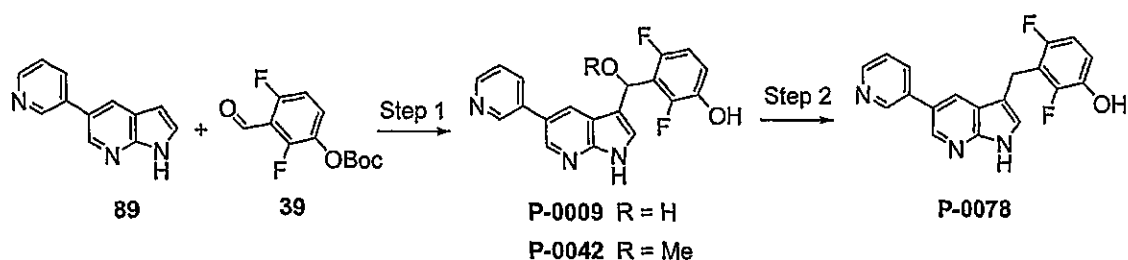


was prepared using the protocol of Scheme 21, substituting hexachloroethane with N-fluoro-N-(phenylsulfonyl) benzenesulfonamide in Step 1. MS(ESI) [M + H]⁺ = 137.1.

Example 10: Synthesis of 2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenol P-0078 and related compounds.

[0240] Compound **P-0078** was synthesized in two steps from 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** as shown in Scheme 24.

Scheme 24



Step 1 – Preparation of 2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenol (P-0009):

[0241] To carbonic acid *tert*-butyl ester 2,4-difluoro-3-formyl-phenyl ester (**39**, 0.405 g, 15.7 mmol) in methanol (36 mL), under an atmosphere of nitrogen, was added 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**89**, 288.0 mg, 14.8 mmol, prepared as described in Example 17) and potassium hydroxide (145.0 mg, 25.9 mmol). The reaction was stirred at room temperature overnight. Then, the reaction was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The mixture was purified by silica gel column chromatography eluting with 4% methanol in methylene chloride to provide two separate compounds, a colorless oil (**P-0009**, 0.23 g, 44.1%, MS(ESI) $[M+H]^+ = 354.1$), and a colorless oil (**P-0042**, 0.050 g, 9.2%, MS(ESI) $[M+H]^+ = 367.1$).

Step 2 – Preparation of 2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenol (P-0078):

[0242] To 2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenol (**P-0009**, 34.0 mg, 0.096 mmol) in acetonitrile (15 mL), were added trifluoroacetic acid (1.0 mL, 13.0 mmol) and triethylsilane (2.0 mL, 12.0 mmol). The reaction was stirred at room temperature for 48 hours. The reaction mixture was poured sodium bicarbonate solution, 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 30% ethyl acetate in hexane to give the compound (**P-0078**, 6.0 mg, 19%). MS(ESI) $[M+H]^+ = 338.1$.

[0243] Additional compounds were prepared following the protocol of Scheme 24, replacing either or both of carbonic acid *tert*-butyl ester 2,4-difluoro-3-formyl-phenyl ester **39** with an appropriate aldehyde and/or 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** with an appropriate azaindole in Step 1.

Azaindoles were purchased or synthesized as described in Examples 6 and 17. Aldehydes were prepared as described in Example 5 (through Step 2). Some compounds were isolated after Step 1, as either hydroxy or methoxy derivatives. The following compounds were made following this procedure:

Propane-2-sulfonic acid {3-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-methoxy-methyl]-2,4-difluoro-phenyl}-amide (**P-0356**),

Propane-2-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenyl]-amide (**P-0867**),

Propane-2-sulfonic acid {2,4-difluoro-3-[methoxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**P-0947**),

Propane-1-sulfonic acid {3-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-2,4-difluoro-phenyl}-amide (**P-0188**),

Propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenyl]-amide (**P-0910**),

Dimethylamino-1-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**P-0944**),

Propane-1-sulfonic acid [2,4-difluoro-3-(5-phenylamino-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-amide (**P-0818**),

Propane-1-sulfonic acid [2,4-difluoro-3-(5-phenyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-amide (**P-0911**),

Propane-1-sulfonic acid [2,4-difluoro-3-(5-morpholin-4-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-amide (**P-0964**),

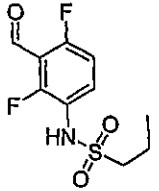
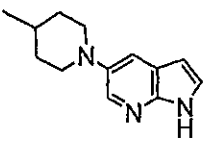
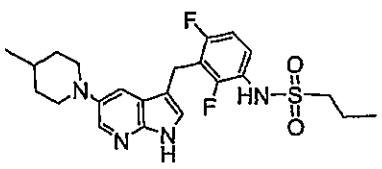
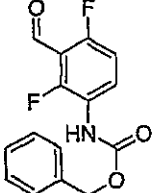
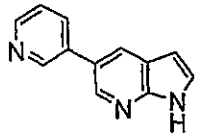
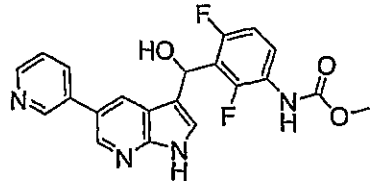
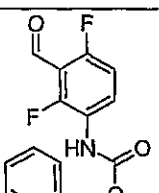
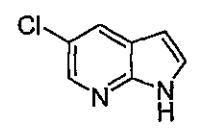
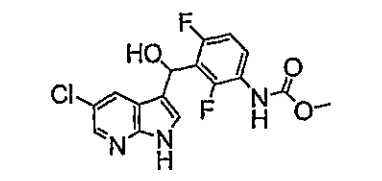
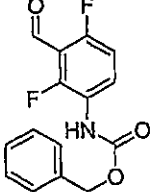
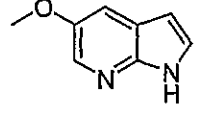
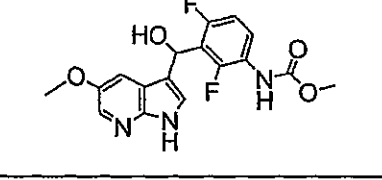
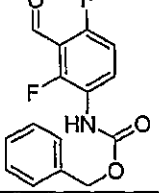
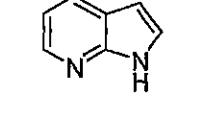
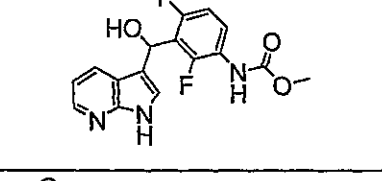
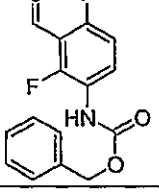
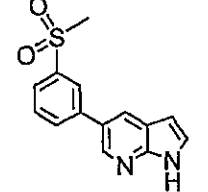
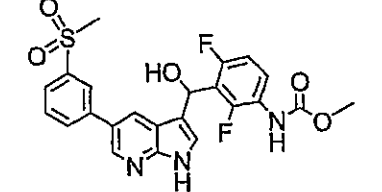
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-methyl-piperidin-1-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-phenyl}-amide (**P-0984**) and

{2,4-Difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-carbamic acid methyl ester (**P-0065**).

The following table indicates the aldehyde (column 2) and azaindole (column 3) used to afford the target compound (column 4). Column 1 provides the compound number and column 5 the observed mass. Compounds isolated after Step 1 of Scheme 24 are so noted in column 1.

	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-0356 Step 1				474.1 476.1

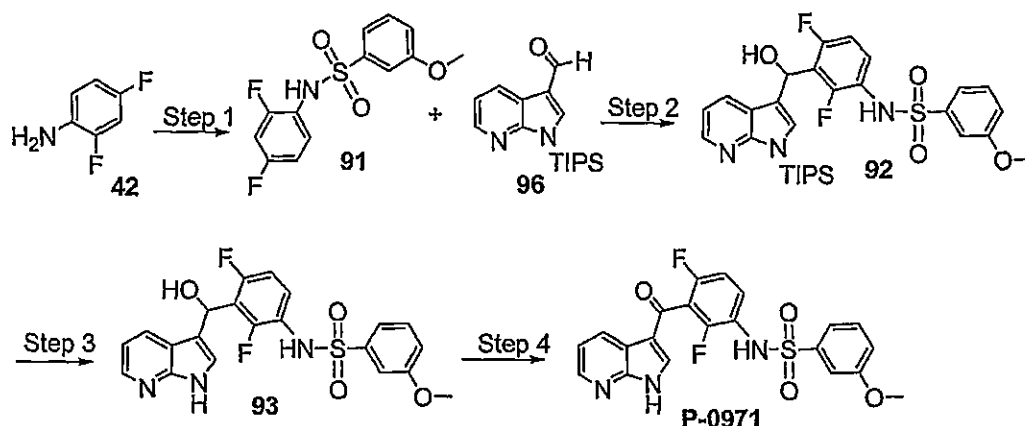
	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-0867				460.2
P-0947 Step 1				459.2
P-0188 Step 1				460 462
P-0910				444.1 446.1
P-0944 Step 1				460.2
P-0818				457.1
P-0911				442.2
P-0964				449.3 [M-H] ⁻

	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-0984				463.3
P-0065 Step 1				
Isolated Step 1				
Isolated Step 1				
Isolated Step 1				
Isolated Step 1				

Example 11: Synthesis of N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl) phenyl]-3-methoxy-benzenesulfonamide P-0971.

[0244] Compound P-0971 was synthesized in four steps from 2,4-difluorophenylamine 42 as shown in Scheme 26.

Scheme 26



Step 1 – Preparation of *N*-(2,4-difluoro-phenyl)-3-methoxy-benzenesulfonamide (91):

[0245] To 2,4-difluoro-phenylamine (42, 0.44 mL, 4.4 mmol) in methylene chloride (10.0 mL), under an atmosphere of nitrogen, were added pyridine (1.00 mL, 12.4 mmol) and 3-methoxy-benzenesulfonyl chloride (1.00 g, 4.84 mmol). After 12 hours, the reaction was poured into cold 1 M HCl 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 20 % ethyl acetate in hexane to give light yellow solid (91, 0.90 g, 69%). MS(ESI)[M+H]⁺ = 300.

Step 2 – Preparation of *N*-{2,4-difluoro-3-[hydroxy-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-3-methoxy-benzenesulfonamide (92):

[0246] To *N*-(2,4-difluoro-phenyl)-3-methoxy-benzenesulfonamide (91, 0.148 g, 0.494 mmol) in tetrahydrofuran (10.0 mL) cooled in a -78 °C acetone/dry ice bath, under an atmosphere of nitrogen, was added lithium diisopropylamide (0.85 M in tetrahydrofuran, 1.45 mL, 1.23 mmol) dropwise. After 30 minutes, 1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (96, 0.15 g, 0.500 mmol, prepared as described in Example 12) was added in tetrahydrofuran (2.0 mL) into the reaction dropwise. Then the reaction was stirred for 1 hour at -78 °C and allowed to reach 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 40 % ethyl acetate in hexane to give light yellow solid (92, 0.080 g, 26.8%). MS(ESI)[M+H]⁺ = 602.

Step 3 – Preparation of *N*-{2,4-difluoro-3-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-phenyl}-3-methoxy-benzenesulfonamide (93):

[0247] To *N*-{2,4-difluoro-3-[hydroxy-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-3-methoxy-benzenesulfonamide (92, 0.075 g, 0.12 mmol) in tetrahydrofuran (3.0

mL), was added tetra-n-butylammonium fluoride (0.039 g, 0.15 mmol). The reaction was stirred at room temperature for 20 minutes. 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 3 % methanol in dichloromethane to give light yellow solid (**93**, 0.030 g, 55%). MS(ESI)[M+H]⁺ = 446.

Step 4 – Preparation of N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]-3-methoxy-benzenesulfonamide (P-0971):

[0248] To N-{2,4-difluoro-3-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-phenyl}-3-methoxy-benzenesulfonamide (**93**, 0.02 g, 0.05 mmol) in tetrahydrofuran (3.0 mL) was added Dess-Martin periodane (0.02 g, 0.015 mmol) under an atmosphere of nitrogen. The reaction was stirred for 10 minutes 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 3 % methanol in dichloromethane to give light yellow solid (**P-0971**, 0.010 g, 50%). MS(ESI)[M+H]⁺ = 444.

[0249] Additional compounds were prepared following the protocol of Scheme 26, replacing 3-methoxy-benzene sulfonyl chloride with the appropriate sulfonyl chloride in Step 1. The following compounds were made following this procedure:

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,5-dimethoxy-benzenesulfonamide (**P-1131**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-methoxy-benzenesulfonamide (**P-0958**),

Piperidine-1-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0952**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-0931**),

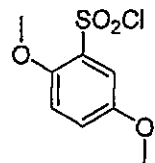
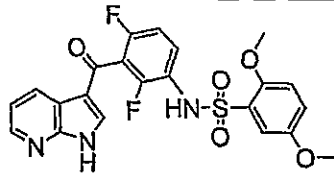
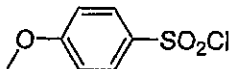
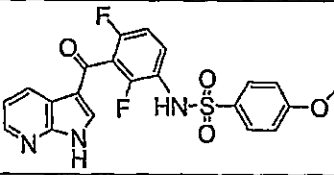
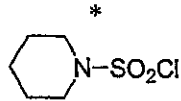
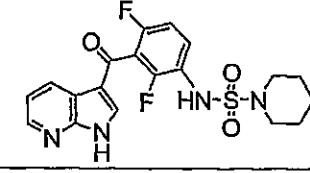
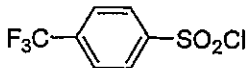
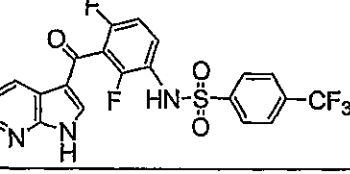
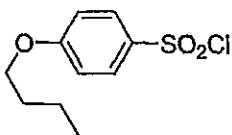
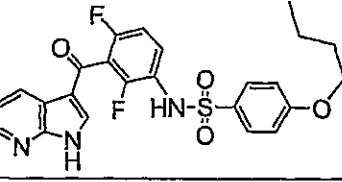
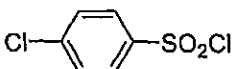
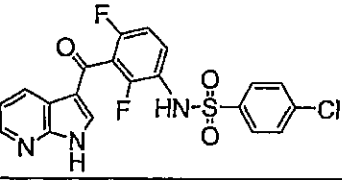
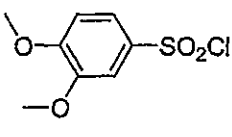
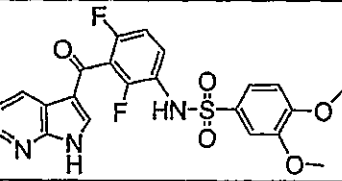
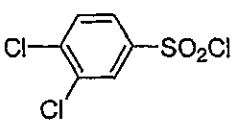
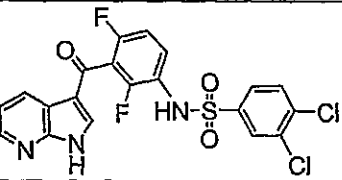
4-Butoxy-N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-1006**),

4-Chloro-N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-0937**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3,4-dimethoxy-benzenesulfonamide, (**P-1090**), and

3,4-Dichloro-N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-1015**).

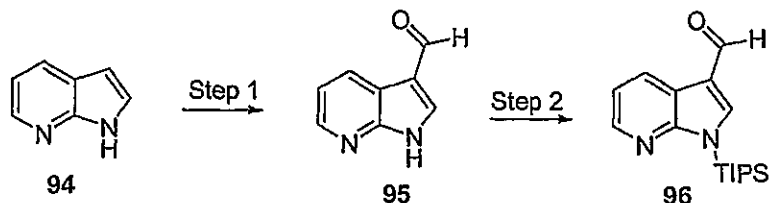
The following table indicates the sulfonyl chloride (column 2) used to afford the target compound (column 3). Column 1 provides the compound number and column 4 gives the observed mass.

	Sulfonyl chloride	Compound	MS(ESI) [M+H] ⁺ observed
P-1131			474.2
P-0958			444.2
P-0952			421.2
P-0931			482.2
P-1006			486.2
P-0937			446.1 [M-H] ⁻
P-1090			474.2
P-1015			480.0 482.1 [M-H] ⁻

* Piperidine-1-sulfonyl chloride prepared from sulfonyl chloride and piperidine in acetonitrile, refluxed for 8 hours, concentrated, and used without further purification.

Example 12: Synthesis of 1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde 96.

[0250] Compound 96 was synthesized in two steps from 7-azaindole 94 as described in Scheme 27.

Scheme 27**Step 1 – Preparation of 1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (95):**

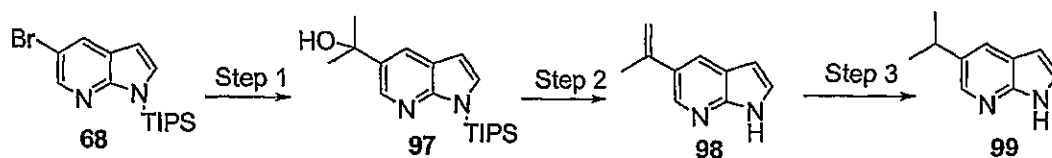
[0251] To 1H-Pyrrolo[2,3-b]pyridine (94, 16.0 g, 135 mmol) in water (110 mL), were added hexamethylenetetramine (26.0 g, 185 mmol), and acetic acid (55.0 mL, 967 mmol). The reaction was refluxed for 12 hours. Water (329 mL) was added and the reaction was cooled to room temperature. The reaction was filtrated and washed with water to give the compound (95, 15.0 g, 76%). MS(ESI)[M+H]⁺ = 147.

Step 2 – Preparation of 1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (96):

[0252] To 1H-Pyrrolo[2,3-b]pyridine-3-carbaldehyde (95, 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 the compound (96, 3.0 g, 36%). MS(ESI)[M+H]⁺ = 303.

Example 13: Synthesis of 5-isopropyl-1H-pyrrolo[2,3-b]pyridine 99.

[0253] Compound 98 was synthesized in three steps from 5-bromo-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine 68 described in Scheme 28.

Scheme 28**Step 1 – Preparation of 2-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-propan-2-ol (97):**

[0254] To 5-bromo-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (68, 2.0 g, 5.66 mmol, prepared as described in Example 6) in tetrahydrofuran (20.0 mL), cooled in a -78 °C acetone/dry ice bath, under an atmosphere of nitrogen, was added tert-butyllithium (1.7 M in tetrahydrofuran, 7.3 mL, 12

mmol) dropwise. After 20 minutes, acetone (0.830 mL, 11 mmol) was added dropwise to the reaction. The reaction was stirred for 30 minutes at -78°C and then allowed to reach 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 the compound (**97**, 1.30 g, 69%). MS(ESI)[$\text{M}+\text{H}^+$] $^+$ = 333.

Step 2 – Preparation of 5-isopropenyl-1H-pyrrolo[2,3-b]pyridine (98):

[0255] To 2-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-propan-2-ol (**97**, 0.500 g, 1.5 mmol) in acetonitrile (10.0 mL) were added triethylsilane (1.00 mL, 6.3 mmol) and trifluoroacetic acid (0.50 mL, 6.5 mmol) under an atmosphere of nitrogen. The reaction was refluxed for 3 hours, then cooled down to 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 50 % ethyl acetate in hexane to give the compound (**98**, 0.200 g, 84%). MS(ESI)[$\text{M}+\text{H}^+$] $^+$ = 159.

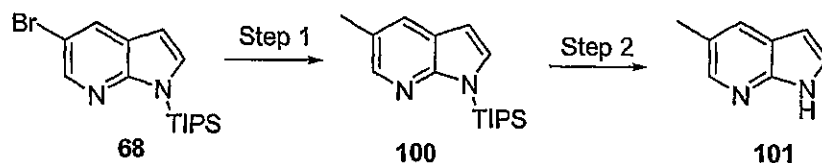
Step 3- Preparation of 5-isopropyl-1H-pyrrolo[2,3-b]pyridine (99):

[0256] To 5-isopropenyl-1H-pyrrolo[2,3-b]pyridine (**98**, 0.080 g, 0.501 mmol) in tetrahydrofuran (5.0 mL) was added 20 % palladium hydroxide on carbon (5.0 mg). The reaction was stirred under hydrogen at 40 psi for 30 minutes. The reaction mixture was filtered and concentrated to give the compound (**99**, 0.078 g, 96%). MS(ESI)[$\text{M}+\text{H}^+$] $^+$ = 161.

Example 14: Synthesis of 5-Methyl-1H-pyrrolo[2,3-b]pyridine 101.

[0257] Compound **101** was synthesized in two steps from 5-bromo-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine **68** described in Scheme 29.

Scheme 29



Step 1 – Preparation of 5-Methyl-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (100):

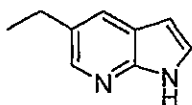
[0258] To $\text{PdCl}_2(\text{dppf})$ (0.04 g, 0.05 mmol) in toluene (10.0 mL) under an atmosphere of nitrogen were added 5-bromo-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (**68**, 0.3 g, 0.8 mmol, prepared as described in Example 6, 1.0 mL in toluene) and methylmagnesium bromide (1.0 M in tetrahydrofuran, 3.0 mL, 3.0 mmol). The reaction was stirred 90°C for 2 hours and then allowed to reach to room temperature. The reaction was poured into citric acid (0.1 M in 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 50 % ethyl acetate in hexane to give the compound (**100**, 0.16 g, 60.0 %). MS(ESI)[M+H]⁺ = 289.4.

*Step 2 – Preparation of 5-Methyl-1H-pyrrolo[2,3-b]pyridine (**101**):*

[0259] To 5-Methyl-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (**100**, 0.160 g, 0.55 mmol) in tetrahydrofuran (3.0 mL) was added tetra-n-butylammonium fluoride (0.145 g, 0.55 mmol). The reaction was stirred for 1 hour 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 3% methanol in dichloromethane to provide light yellow solid (**101**, 0.07 g, 95%). MS(ESI)[M+H]⁺ = 133.2.

[0260] 5-Methyl-1H-pyrrolo[2,3-b]pyridine

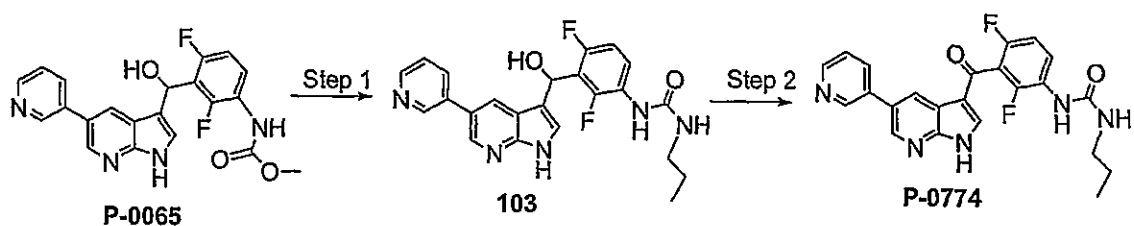


was prepared following the protocol of Scheme 29, substituting methylmagnesium bromide with ethylmagnesium bromide in Step 1.

Example 15: Synthesis of 1-[2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-propyl-urea P-0774 and related compounds.

[0261] Compound P-0774 was synthesized in two steps from {2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3b]pyridin-3-yl)-methyl]-phenyl}-carbamic acid methyl ester P-0065 described in Scheme 30.

Scheme 30



Step 1 – Preparation of 1-{2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3b]pyridin-3-yl)-methyl]-phenyl}-3-propyl-urea (103):

[0262] To {2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3b]pyridin-3-yl)-methyl]-phenyl}-carbamic acid methyl ester (**P-0065**, 30.0 mg, 0.07 mmol, prepared as described in Example 10) was added 1-propanamine (2.0 mL, 20 mmol) and the reaction was heated to 120 °C for 20 minutes in a CEM Discover microwave instrument. 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 5% methanol in methylene chloride to give the compound (**103**, 20.0 mg, 60%).

MS(ESI)[M+H]⁺ = 438.51.

Step 2 – Preparation of 1-[2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-propyl-urea (P-0774):

[0263] To 1-{2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3b]pyridin-3-yl)-methyl]-phenyl}-3-propyl-urea (**103**, 20.0 mg, 0.04 mmol) in tetrahydrofuran (3 mL) was added Dess-Martin periodane (23.0 mg, 0.055 mmol) under an atmosphere of nitrogen. The reaction was stirred for 10 minutes. The reaction was concentrated and purified by silica gel column chromatography eluting with 1 % methanol in dichloromethane to give the compound (**P-0774**, 6.0 mg, 30 %).

MS(ESI)[M+H]⁺ = 436.5.

[0264] Additional compounds were prepared following the protocol of Scheme 30, replacing 1-propanamine with an appropriate amine and optionally replacing {2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3b]pyridin-3-yl)-methyl]-phenyl}-carbamic acid methyl ester **P-0065** with an appropriate carbamic acid methyl ester (see Example 10) in Step 1. The following compounds were made following this procedure:

1-sec-Butyl-3-[2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1289**),

1-Cyclopentyl-3-[2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1317**),

1-Butyl-3-[2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1318**),

1-Butyl-3-[2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1567**),

1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-(2-morpholin-4-yl-ethyl)-urea (**P-1580**),

1-Butyl-3-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-urea (**P-1586**),

Morpholine-4-carboxylic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (P-1606),

1-Butyl-3-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-1-methyl-urea (P-1612),

1-Butyl-3-[2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-1-methyl-urea (P-1884),

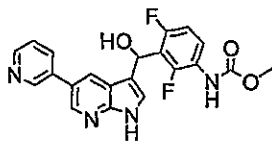
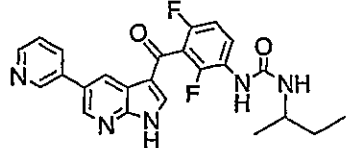
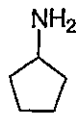
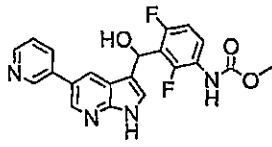
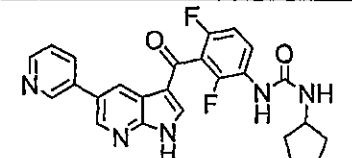
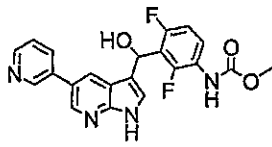
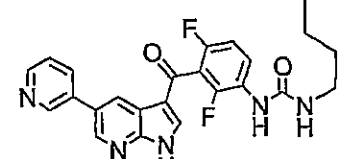
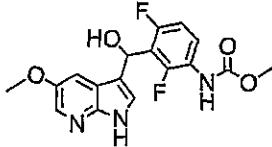
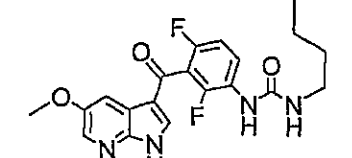
Morpholine-4-carboxylic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (P-1894),

1-Butyl-3-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-1-ethyl-urea (P-1983),

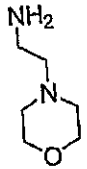
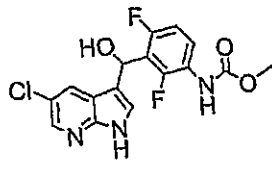
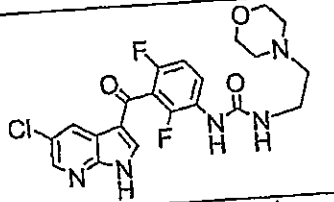
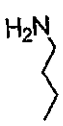
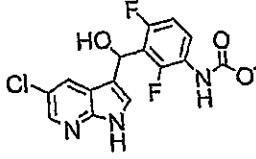
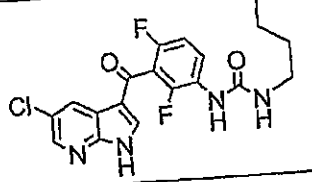
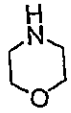
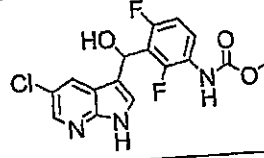
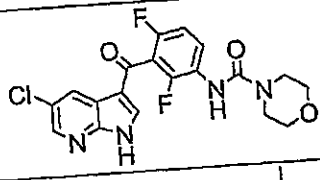
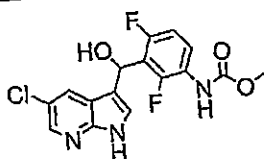
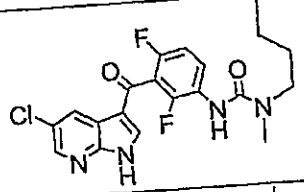
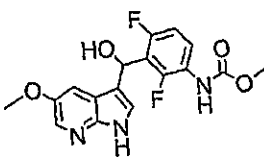
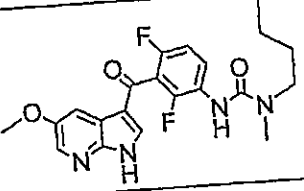
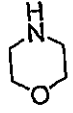
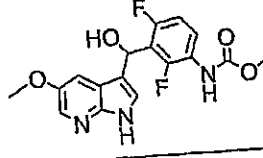
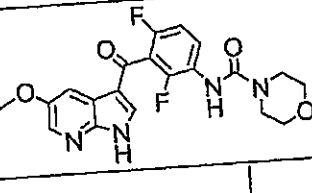
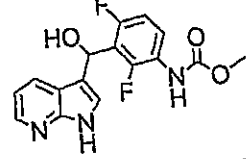
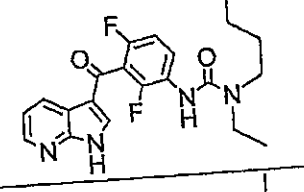
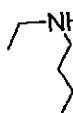
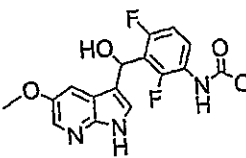
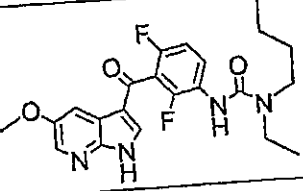
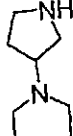
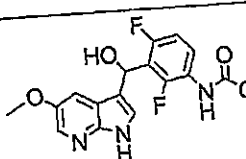
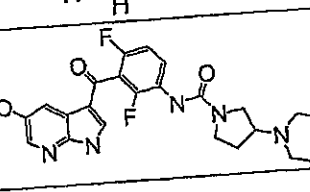
1-Butyl-3-[2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-1-ethyl-urea (P-1994), and

3-Diethylamino-pyrrolidine-1-carboxylic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (P-2015).

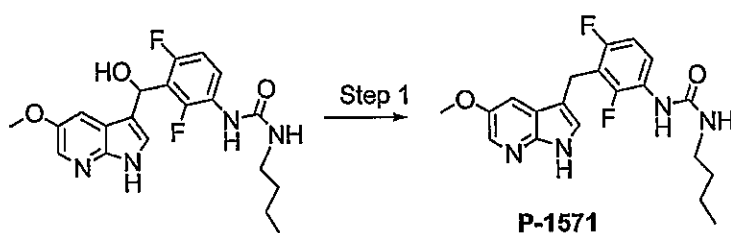
The following table indicates the amine (column 2) and the carbamic acid methyl ester (column 3) used to afford the target compounds (column 4). Column 1 provides the compound number and column 5 the observed mass.

	Amine	Carbamic acid methyl ester	Compound	MS(ESI) [M+H] ⁺ observed
P-1289				450.4
P-1317				462.4
P-1318				450.5
P-1567				403.2

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	Amine	Carbamic acid methyl ester	Compound	MS(ESI) [M+H] ⁺ observed
P-1580				464.3
P-1586				407.3
P-1606				421.1
P-1612				421.3
P-1884				417.4
P-1894				417.4
P-1983				401.4
P-1994				431.4
P-2015				472.4

[0265] The intermediate product of Step 1 of Scheme 30 can alternatively be reacted under reducing conditions to provide analogous compounds in which the carbonyl linker of the 3-position of azaindole to the phenyl ring is methylene. The product of Step 1 is a mixture of the hydroxyl and methoxy methyl linker of the 3-position, which may be carried through the reduction Step as the mixture or may be isolated as either the hydroxyl or methoxy for use in this reaction. This reduction is exemplified as follows using the product of Step 1 in the preparation of **P-1567** to prepare 1-Butyl-3-[2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-urea **P-1571**.



*Step 1 – Preparation of 1-Butyl-3-[2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-urea (**P-1571**):*

[0266] A mixture of 1-Butyl-3-[2,4-difluoro-3-[hydroxy-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl]-urea (41 mg, 0.000081 mol, isolated from Step 1 of Scheme 30), triethylsilane (2 mL, 0.01 mol), and trifluoroacetic acid (1 mL, 0.01 mol) in 20 mL of acetonitrile was refluxed for 3 hrs. The mixture was concentrated and the residue was redissolved in ethyl acetate and sodium bicarbonate solution. The organic layer was collected and dried over MgSO_4 . An off-white solid compound was obtained after chromatography (**P-1571**, 18 mg, 57%). MS(ESI) $[\text{M}-\text{H}]^+ = 389.2$.

[0267] Additional compounds were prepared following the protocol of Step 1 of Scheme 30 followed by the reduction step above as Step 2, where the product of Scheme 30 Step 1 may be isolated as either the hydroxyl or methoxy derivative, or used as the mixture, replacing 1-propanamine with an appropriate amine and {2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-carbamic acid methyl ester **P-0065** with an appropriate carbamic acid methyl ester (see Example 10) in Step 1. The following compounds were made following this procedure:

- 1-Cyclopentyl-3-[2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-urea (**P-1572**),
- 1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenyl]-3-cyclopentyl-urea (**P-1575**),
- 1-Butyl-3-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenyl]-urea (**P-1587**),
- 1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenyl]-3-(2-morpholin-4-yl-ethyl)-urea (**P-1594**),
- Morpholine-4-carboxylic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-

phenyl]-amide (P-1595),

1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenyl]-3-(2,2,2-trifluoroethyl)-urea (P-1601),

1-Cyclopentyl-3-{2,4-difluoro-3-[5-(3-methanesulfonyl-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-phenyl}-urea (P-1615),

1-Butyl-3-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenyl]-1-methyl-urea (P-1625),

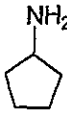
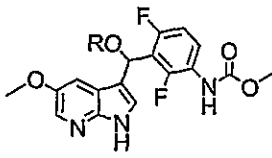
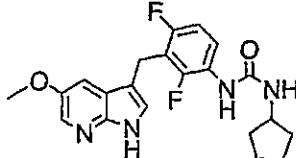
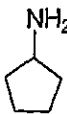
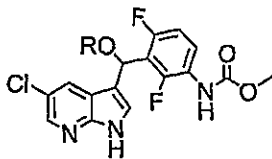
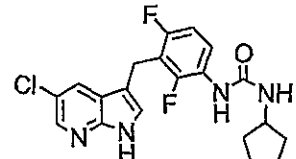
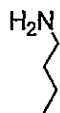
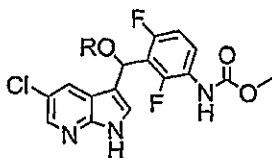
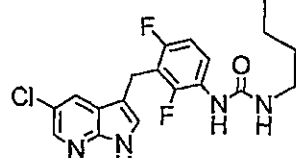
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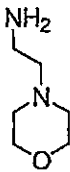
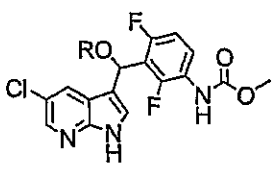
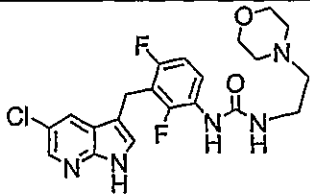
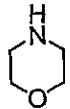
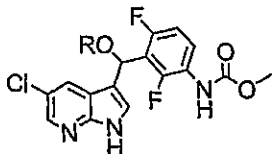
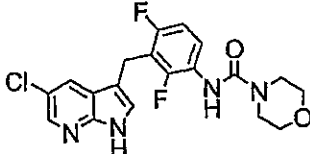
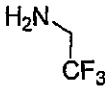
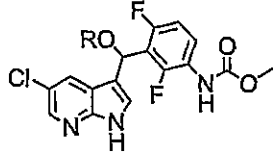
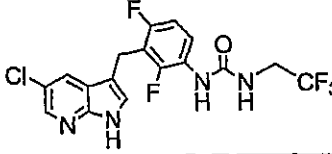
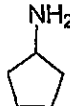
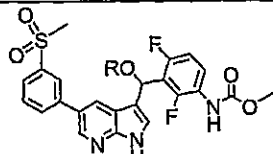
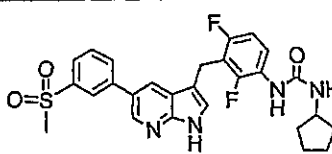
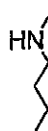
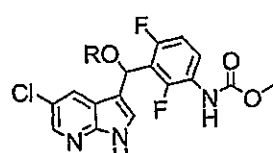
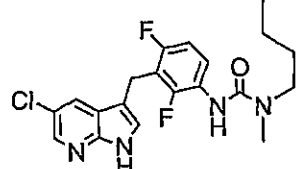
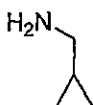
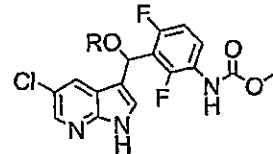
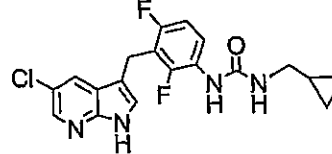
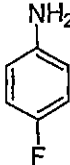
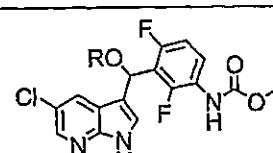
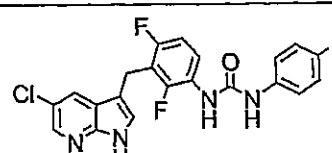
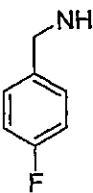
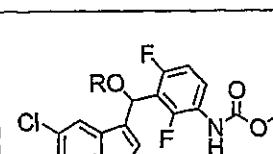
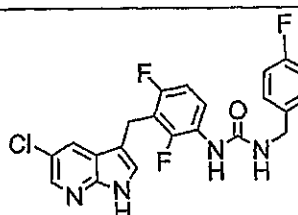
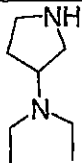
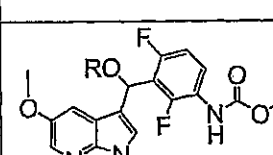
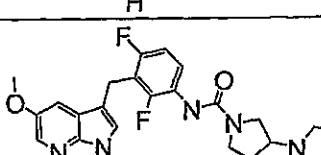
1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenyl]-3-(4-fluoro-phenyl)-urea (P-1657),

1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenyl]-3-(4-fluoro-benzyl)-urea (P-1654), and

3-Diethylamino-pyrrolidine-1-carboxylic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-amide (P-2014).

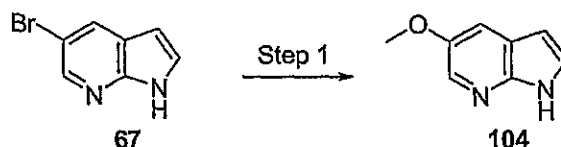
The following table indicates the amine (column 2) and the carbamic acid methyl ester (column 3) used to afford the target compound (column 4). For the carbamic acid methyl ester, R can be H or CH₃, where the compound was either a mixture of the two, or either of the isolated compounds wherein R is H or R is CH₃. Column 1 provides the compound number and column 5 the observed mass.

	Amine	Carbamic acid methyl ester	Compound	MS(ESI) [M+H] ⁺ observed
P-1572				401.2
P-1575				405.2
P-1587				393.3

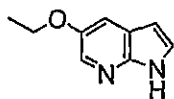
	Amine	Carbamic acid methyl ester	Compound	MS(ESI) [M+H] ⁺ observed
P-1594				450.3
P-1595				407.2
P-1601				419.2
P-1615				525.2
P-1625				407.3
P-1652				391.2
P-1657				461.2
P-1654				445.2
P-2014				458.4

Example 16: Synthesis of 5-Methoxy-1H-pyrrolo[2,3-b]pyridine 104 and related compounds.

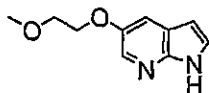
[0268] Compound 104 was synthesized in one step from 5-bromo-1H-pyrrolo[2,3-b]pyridine 67 as described in Scheme 31.

Scheme 31*Step 1 – Preparation of 5-Methoxy-1H-pyrrolo[2,3-b]pyridine (104):*

[0269] To 5-bromo-7-azaindole (67, 500.0 mg, 2.53 mmol) in N,N-dimethylformamide (8 mL) were added copper(I) iodide (966 mg, 5.08 mmol) and sodium methoxide in methanol (3 M, 5 mL). The reaction was stirred overnight at 120 °C under an atmosphere of Argon. The reaction was poured into water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered. The filtrate was concentrated and purified with silica gel column chromatograph eluting with 20% ethyl acetate in hexane to give white solid (104, 140 mg, 28%). MS(ESI)[M+H]⁺ = 149.1. In an alternative method, 2.3 g (11.7 mmol) 5-bromo-7-azaindole (67, 2.3 g, 11.7 mmol) was dissolved in 75 mL N,N-dimethylformamide and 50 mL methanol (50 mL), adding sodium methoxide (32 g, 0.6 mol) and copper-(I) bromide (3.2 g, 22.4 mmol) at room temperature. The reaction was stirred for three hours at 100 °C under an atmosphere of argon. The mixture was diluted with ethyl acetate and poured into a solution of ammonium chloride:ammonium hydroxide (4:1). The organic layer was extracted with ammonium chloride:ammonium hydroxide (4:1), washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The desired compound was isolated by silica gel column chromatography eluting with 30% to 70% ethyl acetate in hexanes to give a yellow solid (104, 0.27 g, 15.6%). MS(ESI) [M + H]⁺ = 149.2.

[0270] 5-Ethoxy-1H-pyrrolo[2,3-b]pyridine 506

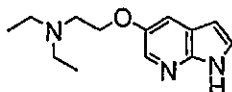
was prepared using the protocol of Scheme 31, substituting methanol with ethanol and sodium methoxide with sodium ethoxide.

[0271] 5-(2-Methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine 507

was prepared using the protocol of Scheme 31, substituting methanol with 2-Methoxy-ethanol and

sodium methoxide with sodium 2-Methoxy-ethoxide (prepared from 2-Methoxy-ethanol and sodium hydride). MS(ESI) $[M + H]^+ = 193.3$.

[0272] Diethyl-[2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-ethyl]-amine **508**

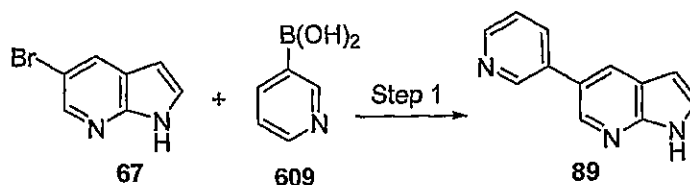


was prepared using the protocol of Scheme 31, substituting methanol with 2-diethylamino-ethanol and sodium methoxide with sodium 2-diethylamino-ethoxide (prepared from 2 2-diethylamino-ethanol and sodium hydride). MS(ESI) $[M + H]^+ = 234.5$.

Example 17: Synthesis of 5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89.**

[0273] 5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** was synthesized in one step from 5-bromo-1H-pyrrolo[2,3-b]pyridine **67** as described in Scheme 32.

Scheme 32



*Step 1 – Preparation of 5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**89**):*

[0274] To 5-bromo-7-azaindole (**67**, 1.00 g, 5.08 mmol) in water (13.0 mL) and acetonitrile (36 mL) were added pyridine-3-boronic acid (**609**, 1.0 g, 8.1 mmol), potassium carbonate (1.79 g, 0.0130 mol) and Tetrakis(triphenylphosphine)palladium(0) (50.0 mg, 0.043 mmol) under an atmosphere of nitrogen. The reaction mixture was heated to 170 °C overnight. 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. The residue was purified with silica gel column chromatography eluting with 25% ethyl acetate in hexane to provide a light yellow solid (**89**, 820 mg, 82%). MS(ESI) $[M + H]^+ = 196.1$.

[0275] Additional compounds were prepared following the protocol of Scheme 32, either by substituting pyridine-3-boronic acid with an appropriate boronic acid or by substituting the 5-bromo-7-azaindole with 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and reacting with a suitable aryl or heteroaryl halide (i.e. coupling with the boronic acid ester on the azaindole, and the halide on the group to be coupled to the 5-position of the azaindole). The following compounds were prepared by this procedure:

5-(4-Chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine (**514**),
 5-(4-Fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine (**605**),
 5-Phenyl-1H-pyrrolo[2,3-b]pyridine,
 5-(6-Methoxy-pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine,
 5-(2-Methoxy-pyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine,
 5-Pyridin-4-yl-1H-pyrrolo[2,3-b]pyridine,
 4-(1H-Pyrrolo[2,3-b]pyridin-5-yl)-benzenesulfonamide,
 3-(1H-Pyrrolo[2,3-b]pyridin-5-yl)-benzenesulfonamide,
 5-Pyrimidin-5-yl-1H-pyrrolo[2,3-b]pyridine,
 5-(3-Methanesulfonyl-phenyl)-1H-pyrrolo[2,3-b]pyridine (**P-0173**), and
 3-(1H-Pyrrolo[2,3-b]pyridin-5-yl)-benzamide (**P-1622**).

The following table indicates either 5-bromo-7-azaindole or 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine starting material (column 1) and the appropriate reagent to be coupled to the 5 position of the azaindole (column 2) to afford the resulting compound (column 3), with the observed mass given in column 4.

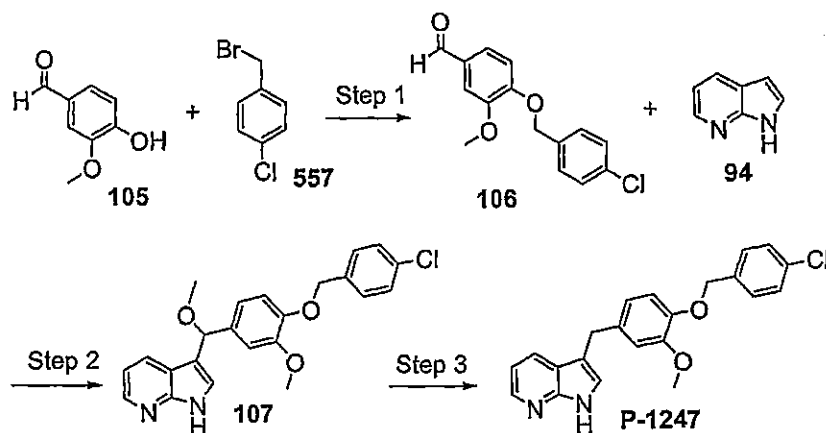
Starting azaindole	Reagent coupled to 5 position	Compound	MS(ESI) [M+H] ⁺ observed
			229.1
			213.1
			195.2
			226.2
			227.2
			196.2

Starting azaindole	Reagent coupled to 5 position	Compound	MS(ESI) [M+H] ⁺ observed
			274.1
			274.1
			197.2
			273.1
			238.2

Example 18: Synthesis of 3-(4-(4-chlorobenzoyloxy)-3-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridine P-1247.

[0276] Compound P-1247 was synthesized in three steps from 4-hydroxy-3-methoxybenzaldehyde 105 as shown in Scheme 33.

Scheme 33



Step 1 – Preparation of 4-(4-chlorobenzoyloxy)-3-methoxybenzaldehyde (106):

[0277] To 4-hydroxy-3-methoxybenzaldehyde (**105**, 600.0 mg, 3.94 mmol) and 4-chlorobenzyl bromide (**557**, 1.20 g, 5.84 mmol) in acetonitrile (6 mL) was added potassium carbonate (0.390 g, 2.82 mmol). The reaction was microwaved on 300 watts, 120 °C for 10 minutes. The reaction was extracted with ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, filtered and the volatiles removed by evaporation. The desired compound was purified by recrystallization from hexanes to provide **106** (1.01 g, 93%). MS(ESI) $[M-H]^+ = 275.1$.

Step 2 – Preparation of 3-((4-(4-chlorobenzoyloxy)-3-methoxyphenyl)(methoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (107):

[0278] To 1H-Pyrrolo[2,3-b]pyridine (**94**, 0.235 g, 1.99 mmol) and 4-(4-chlorobenzoyloxy)-3-methoxybenzaldehyde (**106**, 0.500 g, 1.81 mmol) was added 5 mL of methanol followed by the addition of solid potassium hydroxide (0.203 g, 3.61 mmol). The reaction was allowed to stir at ambient temperature for 18 days. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was separated and volatiles removed to give a solid which was suspended in hot ethyl acetate. The suspension was allowed to cool and the solid collected by vacuum filtration to provide **107** (548 mg, 74%). MS(ESI) $[M+H]^+ = 409.4$.

Step 3 – Preparation of 3-(4-(4-chlorobenzoyloxy)-3-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridine (P-1247):

[0279] To 3-((4-(4-chlorobenzoyloxy)-3-methoxyphenyl)(methoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (**107**, 0.548 g, 1.34 mmol) in acetonitrile (20 mL) was added trifluoroacetic acid (1.7 mL, 2.21 mmol) and triethylsilane (3.47 mL, 2.17 mmol). The reaction was stirred at 60 °C for 15 hours. The volatiles were removed and the desired compound was purified by silica gel chromatography, eluting with a gradient from 0% to 60% ethyl acetate in hexanes to provide a white solid (**P-1247**, 505 mg, 99%). MS(ESI) $[M+H]^+ = 379.4$.

[0280] Additional compounds were prepared using the protocol of Scheme 33, Steps 2 and 3, replacing 4-(4-chlorobenzoyloxy)-3-methoxybenzaldehyde **106** with a suitable aldehyde (prepared as described in Example 34), and optionally replacing 1H-Pyrrolo[2,3-b]pyridine **94** with an appropriate substituted 7-azaindole (see Example 9 or Example 16) in Step 2. The following compounds were made following this procedure:

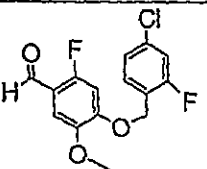
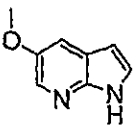
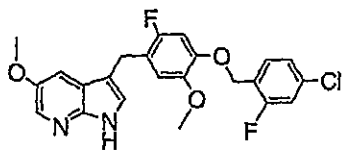
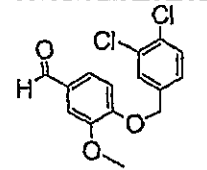
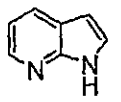
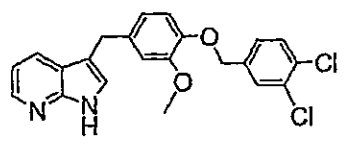
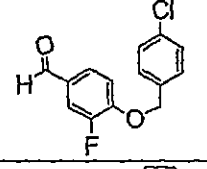
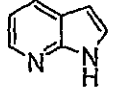
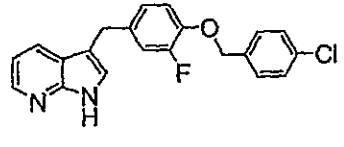
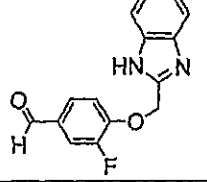
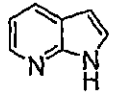
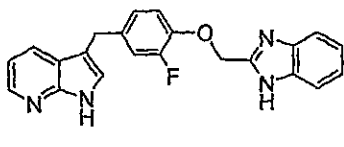
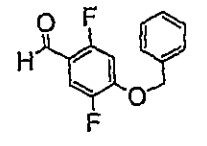
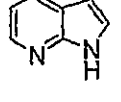
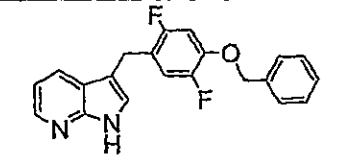
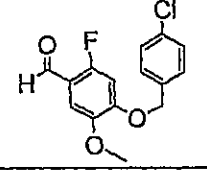
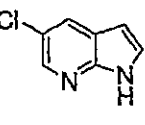
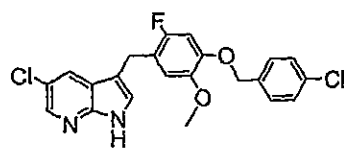
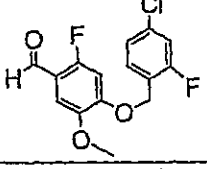
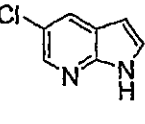
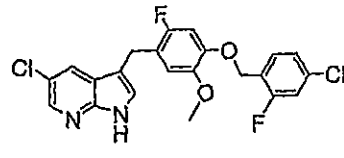
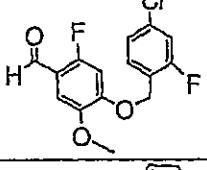
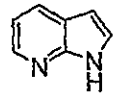
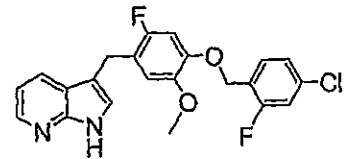
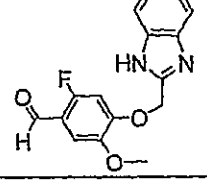
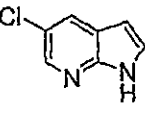
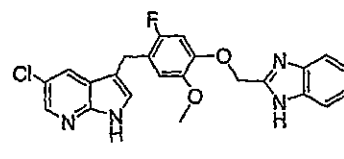
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- 3-[3-Trifluoromethyl-4-(4-trifluoromethyl-benzyloxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (**P-1797**),
- 3-[3-Methoxy-4-[4-(4-methyl-piperazin-1-ylmethyl)-benzyloxy]-benzyl]-1H-pyrrolo[2,3-b]pyridine (**P-1821**),
- 3-[4-(4-Chloro-benzyloxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (**P-1844**),

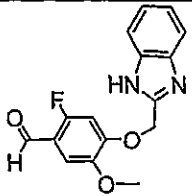
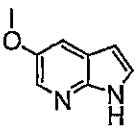
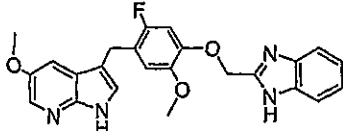
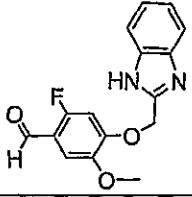
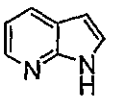
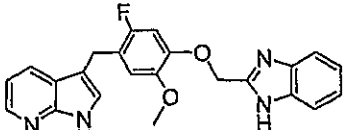
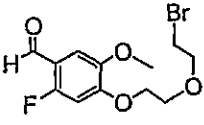
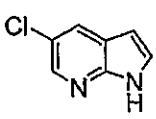
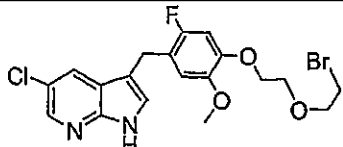
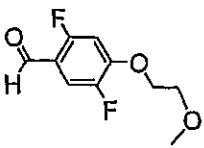
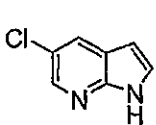
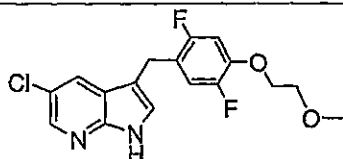
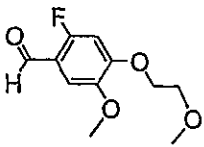
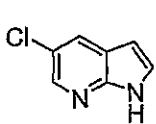
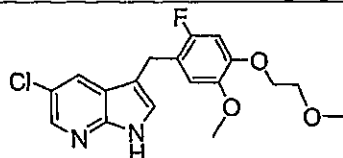
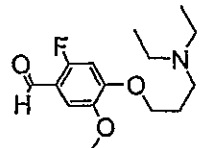
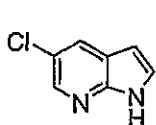
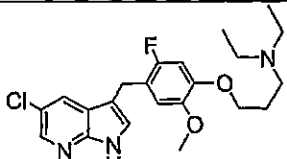
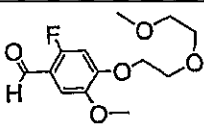
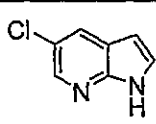
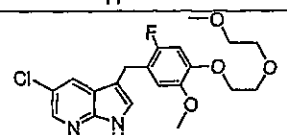
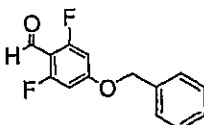
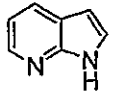
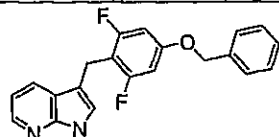
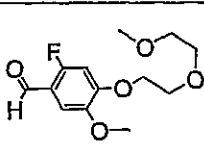
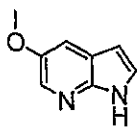
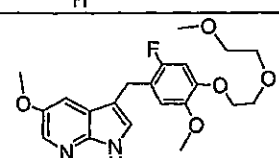
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2-[2-Methoxy-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenoxy-methyl]-1H-benzimidazole (P-1870),
3-[4-(4-Chloro-2-fluoro-benzyloxy)-2-fluoro-5-methoxy-benzyl]-5-methoxy-1H-pyrrolo[2,3-b]pyridine (P-1885),
3-[4-(3,4-Dichloro-benzyloxy)-3-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1886),
3-[4-(4-Chloro-benzyloxy)-3-fluoro-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1896),
2-[2-Fluoro-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenoxy-methyl]-1H-benzimidazole (P-1899),
3-(4-Benzyloxy-2,5-difluoro-benzyl)-1H-pyrrolo[2,3-b]pyridine (P-1901),
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5-Chloro-3-[4-(4-chloro-2-fluoro-benzyloxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1972),
3-[4-(4-Chloro-2-fluoro-benzyloxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1973),
2-[4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-5-fluoro-2-methoxy-phenoxy-methyl]-1H-benzimidazole (P-1976),
2-[5-Fluoro-2-methoxy-4-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenoxy-methyl]-1H-benzimidazole (P-1977),
2-[5-Fluoro-2-methoxy-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenoxy-methyl]-1H-benzimidazole (P-1978),
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5-Chloro-3-[2-fluoro-5-methoxy-4-(2-methoxy-ethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1990),
{3-[4-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-5-fluoro-2-methoxy-phenoxy]-propyl}-diethyl-amine (P-2004),
5-Chloro-3-{2-fluoro-5-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-benzyl}-1H-pyrrolo[2,3-b]pyridine (P-2002),
3-(4-Benzyloxy-2,6-difluoro-benzyl)-1H-pyrrolo[2,3-b]pyridine (P-2022),
3-{2-Fluoro-5-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-benzyl}-5-methoxy-1H-pyrrolo[2,3-b]pyridine (P-2025), and

3-{2-Fluoro-5-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-benzyl}-1H-pyrrolo[2,3-b]pyridine (P-2026).

The following table indicates the aldehyde (column 2) and the azaindole (column 3) used to afford the target compound (column 4). Column 1 indicates the compound number and column 5 the observed mass.

	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1721				413.2
P-1797				451.3
P-1821				457.4
P-1844				397.2
P-1849				432.4
P-1851				
P-1870				385.4

	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1885				445.3
P-1886				413.3
P-1896				367.3
P-1899				373.4
P-1901				351.4
P-1970				431.2
P-1972				449.2
P-1973				415.3
P-1976				437.3

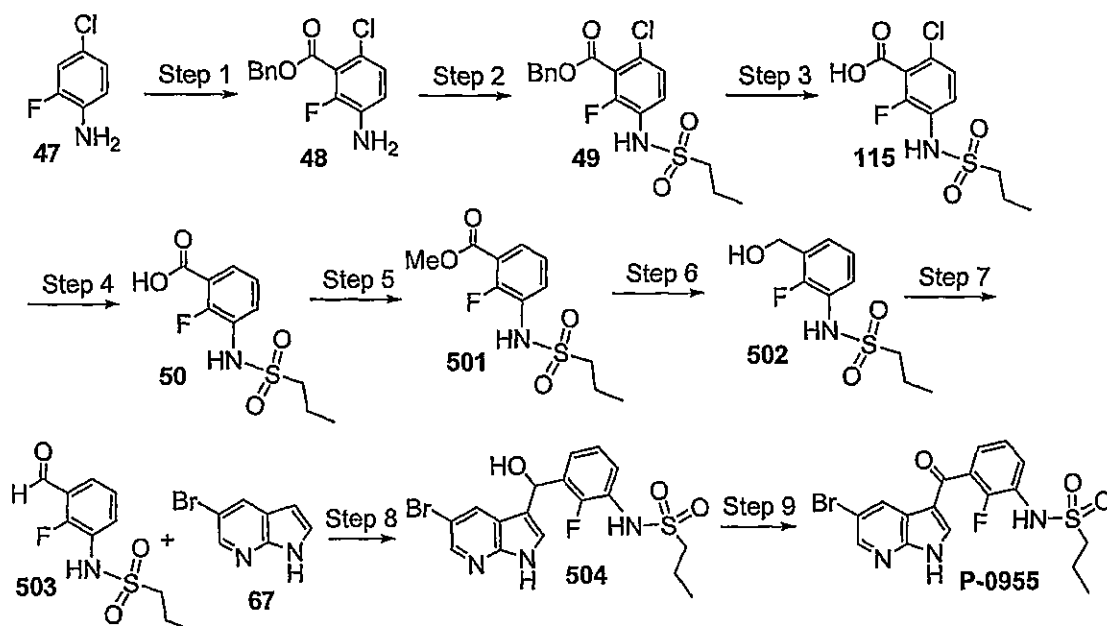
	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1977				433.4
P-1978				403.4
P-1984				457.4 459.4
P-1986				353.4
P-1990				365.3
P-2004				420.4
P-2002				409.3
P-2022				438.1
P-2025				405.2

	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-2026				373.2

Example 19: Synthesis of Propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide P-0955 and related compounds.

[0281] As an alternative method to that of Example 2, compound P-0955 was synthesized in nine steps from 4-chloro-2-fluoro-phenylamine 47 as shown in Scheme 37.

Scheme 37



Step 1 – Preparation of 3-Amino-6-chloro-2-fluoro-benzoic acid benzyl ester (48):

[0282] To 4-chloro-2-fluoro-phenylamine (47, 6.30 mL, 57.0 mmol) in tetrahydrofuran (300 mL), cooled with dry ice/acetone bath under an atmosphere of nitrogen, *n*-butyllithium (2.50 M in hexane, 24.4 mL) was added slowly. After 20 minutes, 1,2-Bis-(chloro-dimethyl-silanyl)-ethane (12.9 g, 60.0 mmol) dissolved in tetrahydrofuran (40.0 mL) was added slowly to the reaction. After 1 hour, *n*-butyllithium (2.50 M in hexane, 25.0 mL) was added slowly to the reaction. The reaction was stirred at -78 °C for 20 minutes and then allowed to warm to room temperature over 60 minutes. The reaction was cooled to -78 °C, followed by addition of *n*-butyllithium (2.50 M in hexane, 26.0 mL)

slowly. After 80 minutes, benzyl chloroformate (10.0 mL, 70.0 mmol) was added to the reaction. The reaction mixture was stirred at -78 °C overnight followed by addition of water (80 mL) and concentrated hydrochloric acid (25 mL). The reaction was allowed to warm to room temperature for 2 hours. The organic layer was separated. The aqueous layer was basified with potassium carbonate and extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The desired compound was isolated by silica gel column chromatography (ethyl acetate/hexane 20%) to give a colorless oil (**48**, 12.5 g, 78.3%). MS(ESI) $[M+H]^+ = 280.0$.

Step 2 – Preparation of 6-chloro-2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid benzyl ester (49):

[0283] To 3-amino-6-chloro-2-fluoro-benzoic acid benzyl ester (**48**, 1.20 g, 4.3 mmol) in methylene chloride (28 mL) was added pyridine (0.52 mL, 6.4 mmol) and propanesulfonyl chloride (0.685 g, 4.8 mmol). 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 anhydrous sodium sulfate, filtered and concentrated. The desired compound was isolated with silica gel column chromatography to give a colorless oil (**49**, 960 mg, 58.0%). MS(ESI) $[M-H]^+ = 384.1$.

Step 3 – Preparation of 6-chloro-2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid (115):

[0284] To 6-chloro-2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid benzyl ester (**49**, 6.00 g, 15.6 mmol) in tetrahydrofuran (100 mL) was added 1.0 M aqueous potassium hydroxide (100 mL). The reaction was heated to reflux overnight. The reaction was poured into water, acidified to pH 2 with 1 N hydrochloric acid and extracted with ethyl acetate. The organic portion was dried over anhydrous sodium sulfate, filtered and concentrated to give a white solid **115** (3.95 g, 85.8%).

Step 4 – Preparation of 2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid (50):

[0285] To 6-chloro-2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid (**115**, 0.69 g, 2.3 mmol) in methanol (10 mL) was added 20% palladium hydroxide on carbon (200 mg). The reaction was stirred under hydrogen at 50 psi for 2 hours. The reaction was filtered and concentrated to give white solid **50** that was used in the next step. MS(ESI) $[M-H]^+ = 260.1$.

Step 5 – Preparation of 2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid methyl ester (501):

[0286] To a 2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid (**50**, 5.05 g, 0.0193 mol) in methylene chloride (100 mL) was added N,N-dimethylformamide (0.075 mL, 0.97 mmol) under an atmosphere of nitrogen. The reaction was cooled with ice/water, followed by slow addition of Oxalyl chloride (2.00 M of in methylene chloride, 10.8 mL, 21.6 mmol). The reaction mixture was stirred at room temperature for 3.0 hours. The reaction was cooled with ice/water, followed by addition of methanol (36.0 mL, 0.89 mol) slowly. The reaction was stirred at room temperature overnight. The

reaction was concentrate and purified with silica gel column chromatography eluting with 30% ethyl acetate in hexane to give a crude white solid 4.0g.

Step 6 – Preparation of Propane-1-sulfonic acid (2-fluoro-3-hydroxymethyl-phenyl)-amide (502):

[0287] To 2-fluoro-3-(propane-1-sulfonylamino)-benzoic acid methyl ester (501, 3.80 g, 13.8 mmol) in tetrahydrofuran (133 mL) was added lithium tetrahydroaluminate (1.00 M in tetrahydrofuran, 20.0 mL, 20.0 mmol) under an atmosphere of nitrogen at room temperature. The reaction was stirred at room temperature for 8 hours, followed by addition of 10 g of NaSO₄·10H₂O. After 12 hours, the reaction was filtered, concentrated and purified with silica gel column chromatography eluting with 5% methanol in methylene chloride to give a white solid (502, 3.0 g, 87.9%).

Step 7 – Preparation of propane-1-sulfonic acid (2-fluoro-3-formyl-phenyl)-amide (503):

[0288] To propane-1-sulfonic acid (2-fluoro-3-hydroxymethyl-phenyl)-amide (502, 0.20 g, 0.81 mmol) in tetrahydrofuran (5.0 mL) was added Dess-Martin periodinane (0.377 g, 0.89 mmol). The reaction was stirred at room temperature 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% ethyl acetate in hexane to give a white solid (503, 100 mg, 50.0%). MS(ESI) [M-H]⁺ = 244.1.

Step 8 – Preparation of Propane-1-sulfonic acid {3-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-2-fluoro-phenyl}-amide (504):

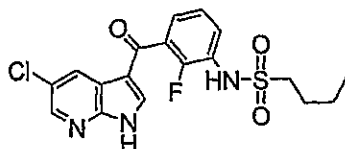
[0289] To 5-bromo-7-azaindole 67 (312 mg, 1.58 mmol) in methanol (28 mL) were added propane-1-sulfonic acid (2-fluoro-3-formyl-phenyl)-amide (503, 370 mg, 1.5 mmol) and potassium hydroxide (422.8 mg, 7.5 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give the desired compound as white solid (504, 300 mg, 45.0%).

Step 9 - Preparation of propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (P-0955):

[0290] To Propane-1-sulfonic acid {3-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-2-fluoro-phenyl}-amide (504, 0.650 g, 1.47 mmol) in tetrahydrofuran (25.0 mL) cooled with ice/water was added Dess-Martin periodinane (0.748 g, 1.76 mmol). The reaction was stirred at room temperature for 15 minutes. The reaction was poured into water containing 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% ethyl acetate in hexane and washed with ethyl acetate to give white solid. (**P-0955**, 0.35 g, 54.1%). MS(ESI) $[M+H]^+ = 460.0, 462.0$.

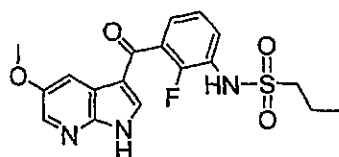
[0291] Butane-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide **P-1250**



was prepared following the protocol of Scheme 37, substituting propane-2-sulfonyl chloride with butane-1-sulfonyl chloride in Step 1 and 5-bromo-1H-pyrrolo[2,3-b]pyridine **67** with 5-chloro-1H-pyrrolo[2,3-b]pyridine **80** (see Example 9) in step 8.

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

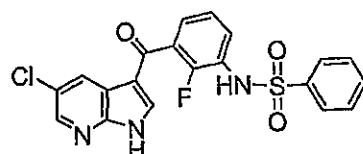
[0292] Propane-1-sulfonic acid [2-fluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide **P-1256**



was prepared following the protocol of Scheme 37, substituting 5-bromo-1H-pyrrolo[2,3-b]pyridine **67** with 5-methoxy-1H-pyrrolo[2,3-b]pyridine **104** (see Example 16) in step 8.

MS(ESI) $[M - H]^+ = 390.1$.

[0293] N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl] benzenesulfonamide **P-1255**

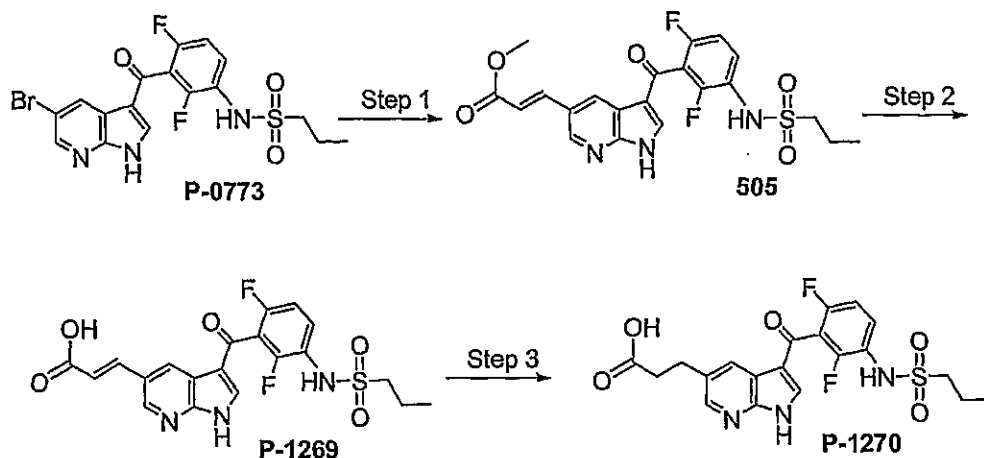


was prepared following the protocol of Scheme 37, substituting propane-2-sulfonyl chloride with benzenesulfonyl chloride in Step 1 and 5-bromo-1H-pyrrolo[2,3-b]pyridine **67** with 5-chloro-1H-pyrrolo[2,3-b]pyridine **80** (see Example 9) in step 8. MS(ESI) $[M - H]^+ = 428.0$.

Example 20: Synthesis of 3-3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl-propionic acid P-1270.

[0294] Compound **P-1270** was synthesized in three steps from propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide **P-0773** as shown in Scheme 38.

Scheme 38



Step 1 – Preparation of (E)-3-3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl-acrylic acid methyl ester (505):

[0295] To propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0773**, 125.0 mg, 0.27 mmol, prepared as described in Example 4) in N,N-dimethylformamide (4.0 mL) were added palladium acetate (15 mg, 0.068 mmol), triphenylphosphine (36 mg, 0.14 mmol), methyl acrylate (0.098 mL, 1.1 mmol) and triethylamine (0.114 mL, 0.82 mmol) under an atmosphere of nitrogen. The reaction was stirred at 140 °C overnight, then poured into water, acidified with water and extracted with ethyl acetate. To the filtrate in methylene chloride (5.0 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.50 mL, 3.3 mmol). The reaction was stirred at room temperature for 3 hours. The reaction was concentrated and purified with silica gel column chromatography eluting with 30% ethyl acetate in hexane to give a light yellow oil that was used directly in the next step.

Step 2 – Preparation of 3-3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl-acrylic acid (P-1269):

[0296] To (E)-3-3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl-acrylic acid methyl ester (100.0 mg, 0.22 mmol) in tetrahydrofuran (5.0 mL) and water (1.50 mL) was added lithium hydroxide (21 mg, 0.86 mmol). The reaction was stirred at room temperature overnight. The reaction was poured into water, acidified with 1N HCl to pH around 1, and then

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 (**P-1269**, 30 mg). MS(ESI) $[M-H]^+ = 448.0$.

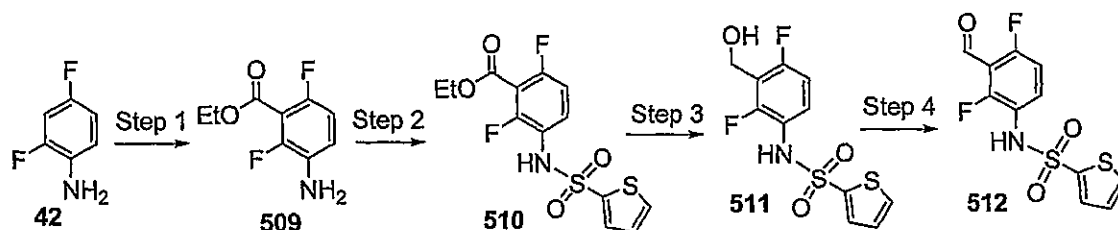
*Step 3 – 3-3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3 -b]pyridin-5-yl-propionic acid (**P-1270**):*

[0297] To 3-3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3 -b]pyridin-5-yl-acrylic acid (**P-1269**, 20.0 mg, 0.045 mmol) in methanol (5.0 mL) was added 20% Pd(OH)₂/C (10 mg) under an atmosphere of hydrogen. The reaction was stirred at room temperature for 2 hours. The reaction mixture was filtered, concentrated and purified with silica gel column chromatography eluting with 10% methanol in methylene chloride to give a white solid (**P-1270**, 8.8 mg). MS(ESI) $[M-H]^+ = 450.1$.

Example 21: Synthesis of thiophene-2-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide 508.

[0298] Compound **512** was synthesized in four steps from 2,4-difluorophenylamine **42** as shown in Scheme 39.

Scheme 39



Step 1 – Preparation of 3-amino-4,2-difluoro-benzoic acid ethyl ester (509):

[0299] To 4,2-difluoro-phenylamine (**42**, 6.30 mL, 57.0 mmol) in tetrahydrofuran (300 mL), cooled with dry ice/acetone bath under an atmosphere of nitrogen, n-butyllithium (2.50 M in hexane, 24.4 mL) was added slowly. After 20 minutes, 1,2-Bis-(chloro-dimethyl-silanyl)-ethane (12.9 g, 60.0 mmol) dissolved in tetrahydrofuran (40.0 mL) was slowly added to the reaction. After 1 hour, n-butyllithium (2.50 M in hexane, 25.0 mL) was slowly added to the reaction. The reaction was stirred at -78 °C for 20 minutes and then allowed to warm to room temperature over 60 minutes. The reaction was cooled to -78 °C, followed by addition of n-butyllithium (2.50 M in hexane, 26.0 mL) slowly. After 80 minutes, ethyl chloroformate (6.69 mL, 70.0 mmol) was added to the reaction. The reaction mixture was stirred at -78 °C overnight followed by addition of water (80 mL) and concentrated hydrochloric acid (25 mL). The reaction was allowed to warm to room temperature for 2 hours. The organic layer was separated. The aqueous layer was basified with potassium carbonate and extracted with ethyl acetate. The organic layers were combined and washed with brine, dried

over anhydrous sodium sulfate, filtered and concentrated. The desired compound was isolated by silica gel column chromatography (ethyl acetate/hexane 20%) to give a colorless oil (**509**, 4.6 g, 39%). MS(ESI) $[M + H]^+ = 218.1$.

*Step 2 – Preparation of 2,6-difluoro-3-(thiophene-2-sulfonylamino)-benzoic acid ethyl ester (**510**):*

[0300] To 3-amino-2,4-difluoro-benzoic acid ethyl ester (**509**, 1.20 g, 5.93 mmol) in methylene chloride (28 mL) was added pyridine (0.52 mL, 6.4 mmol) and thiophene-2-sulfonyl chloride (0.97 g, 5.38 mmol). 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 anhydrous sodium sulfate, filtered and concentrated. The desired compound was isolated with silica gel column chromatography (ethyl acetate/hexane 20%) to give a colorless oil (**510**, 1.2 g, 65.0%). MS(ESI) $[M + H]^+ = 348.2$.

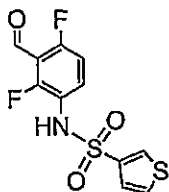
*Step 3 – Preparation of thiophene-2-sulfonic acid (2,4-difluoro-3-hydroxymethyl-phenyl)-amide (**511**):*

[0301] To 2,6-difluoro-3-(thiophene-2-sulfonylamino)-benzoic acid ethyl ester (**510**, 1.6 g, 3.5 mmol) in tetrahydrofuran (25.0 mL) was added lithium tetrahydroaluminate (1.00 M in tetrahydrofuran, 8.08 mL, 8.08 mmol) under an atmosphere of nitrogen at room temperature. The reaction was stirred at room temperature for 8 hours, followed by addition of 10 g of $\text{NaSO}_4 \cdot 10\text{H}_2\text{O}$. After 12 hours, the reaction was filtered, concentrated and purified with silica gel column chromatography eluting with 5% methanol in methylene chloride to give a white solid (**511**, 300.0 mg, 21.0%).

*Step 4 – Preparation of thiophene-2-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (**512**):*

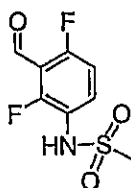
[0302] To thiophene-2-sulfonic acid (2,4-difluoro-3-hydroxymethyl-phenyl)-amide (**511**, 0.46 g, 1.52 mmol) in tetrahydrofuran (5.0 mL) was added Dess-Martin periodinane (0.71 g, 1.67 mmol). The reaction was stirred at room temperature for 10 minutes, then poured into water and extracted with ethyl 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% ethyl acetate in hexane to give a white solid (**512**, 100 mg, 21%). MS(ESI) $[M + H]^+ = 304.2$.

[0303] Thiophene-3-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **513**



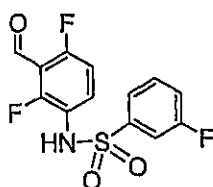
was prepared following the protocol of Scheme 39, substituting thiophene-2-sulfonyl chloride with thiophene-3-sulfonyl chloride in Step 2. MS(ESI) $[M + H]^+ = 304.2$.

[0304] N-(2,4-Difluoro-3-formyl-phenyl)-methanesulfonamide **577**



was prepared following the protocol of Scheme 39, substituting thiophene-2-sulfonyl chloride with methanesulfonyl chloride in Step 2.

[0305] N-(2,4-Difluoro-3-formyl-phenyl)-3-fluoro-benzenesulfonamide **578**

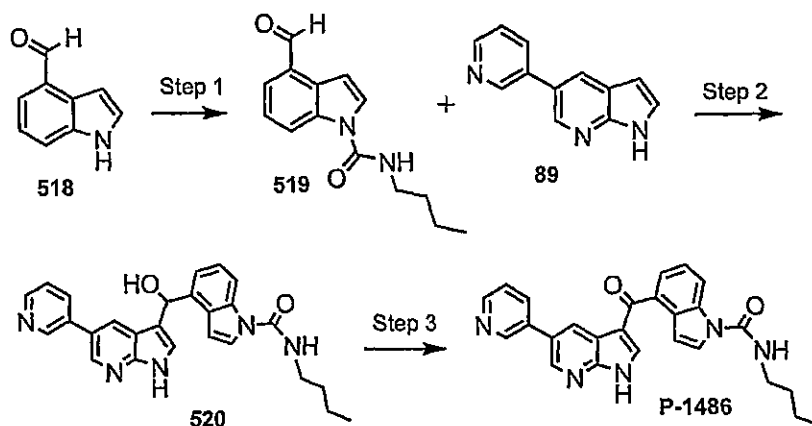


was prepared following the protocol of Scheme 39, substituting thiophene-2-sulfonyl chloride with 3-fluoro-benzenesulfonyl chloride in Step 2.

Example 22: Synthesis of 4-(5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid butylamide P-1486 and related compounds

[0306] Compound **P-1486** was synthesized in three steps from 1H-indole-4-carbaldehyde **518** as shown in Scheme 41.

Scheme 41



Step 1 – Preparation of 4-Formyl-indole-1-carboxylic acid butylamide (519):

[0307] To 1H-Indole-4-carbaldehyde (**518**, 1.57 g, 10.8 mmol) in acetonitrile (20 mL) was added 1-isocyanatobutane (1.81 mL, 16.2 mmol), followed by 4-dimethylaminopyridine (130 mg, 1.1 mmol). The reaction was refluxed for 48 hours. The reaction solution was quenched with 1 M HCl (aq.) and

extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtrated and concentrated to give a light yellow solid (**519**, 2.62 g, 45%). MS(ESI) $[M+H]^+ = 245.2$.

Step 2 – Preparation of 4-[Hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-indole-1-carboxylic acid butylamide (520):

[0308] To 5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**89**, 51 mg, 0.26 mmol, prepared as in Example 17) in methanol (2 mL), was added 4-Formyl-indole-1-carboxylic acid butylamide (**519**, 84 mg, 0.34 mmol) and potassium hydroxide (44 mg, 0.78 mmol). The reaction was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtrated and concentrated. The desired compound was isolated with silica gel column chromatography to give an off-white solid (**520**, 7 mg, 6 %). MS(ESI) $[M+H]^+ = 440.3$.

Step 3 – Preparation of 4-(5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid butylamide (P-1486):

[0309] To 4-[Hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-indole-1-carboxylic acid butylamide (**520**, 7 mg, 0.016 mmol) in tetrahydrofuran (1 mL) was added Dess-Martin periodinane (7.4 mg, 0.017 mmol). The reaction was stirred at room temperature for 30 minutes, then poured into water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtrated and concentrated. The desired compound was purified by Prep HPLC using a gradient of buffer A (5% acetonitrile, 95% water, 0.1% formic acid) and buffer B (95% acetonitrile, 5% water, 0.1% formic acid). **P-1486** was isolated as a fluffy white solid (2.8 mg, 40%). MS(ESI) $[M+H]^+ = 438.3$.

[0310] Additional compounds were prepared following the protocol of Scheme 41, optionally substituting 1-isocyanatobutane with an appropriate isocyanate in Step 1 and optionally substituting 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** with a suitable 7-azaindole in Step 2. The azaindole was purchased or synthesized as described in Examples 16 and 17. The following compounds were made following this procedure:

4-(5-Phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid butylamide (**P-1576**),

4-[5-(4-Chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-indole-1-carboxylic acid butylamide (**P-1602**),

4-(5-Phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid benzylamide (**P-1611**),

4-[5-(4-Chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-indole-1-carboxylic acid benzylamide (**P-1618**),

4-(5-Bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid butylamide (P-1687),
 4-[5-(4-Sulfamoyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-indole-1-carboxylic acid butylamide (P-1854),
 4-[5-(3-Sulfamoyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-indole-1-carboxylic acid butylamide (P-1858),
 4-[5-(2-Methoxy-pyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-indole-1-carboxylic acid butylamide (P-1860),
 4-(5-Pyrimidin-5-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid butylamide (P-1862),
 4-(5-Methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid butylamide (P-1875), and
 4-[5-(6-Methoxy-pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-indole-1-carboxylic acid (pyridin-3-ylmethyl)-amide (P-1887).

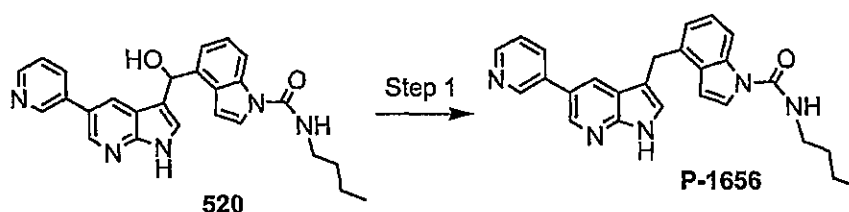
The following table indicates the isocyanate used in Step 1 (column 2), and the 7-azaindole used in Step 2 (column 3) to afford the target compound (column 4). Column 1 provides the compound number and column 5 the observed mass.

	Isocyanate	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1576				437.3
P-1602				471.2
P-1611				471.3
P-1618				505.2
P-1687				439.2 441.2
P-1854				514.2 [M-H] ⁺

	Isocyanate	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1858				516.2
P-1860				469.3
P-1862				439.3
P-1875				391.4
P-1887				503.4

[0311] The product of Step 2 of Scheme 41 can alternatively be reacted to form the corresponding compounds with methylene linker at the 3 position of the azaindole. For example, 4-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-indole-1-carboxylic acid butylamide **P-1656** was prepared from 4-[Hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-indole-1-carboxylic acid butylamide **520** as shown in Scheme 41a.

Scheme 41a

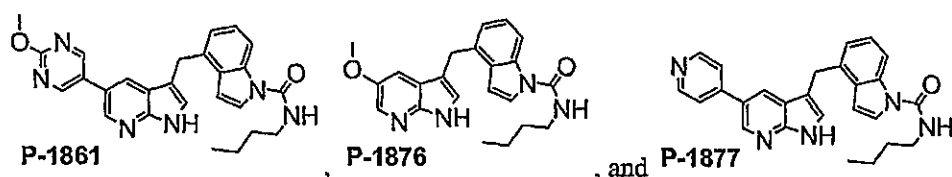


Step 1 – Preparation of 4-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-indole-1-carboxylic acid butylamide (P-1656):

[0312] A mixture of 4-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-indole-1-carboxylic acid butylamide (**520**, 18 mg, 0.041 mmol), trifluoroacetic acid (0.5 mL), triethylsilane (1 mL), and acetonitrile (8 mL) was refluxed for 4 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtrated and concentrated. The desired compound was purified by Prep HPLC using a gradient of buffer A (5% acetonitrile, 95% water, 0.1% formic

acid) and buffer B (95% acetonitrile, 5% water, 0.1% formic acid). **P-1656** was isolated as an off-white solid (4.8 mg, 28%). MS(ESI) $[M+H]^+ = 424.2$.

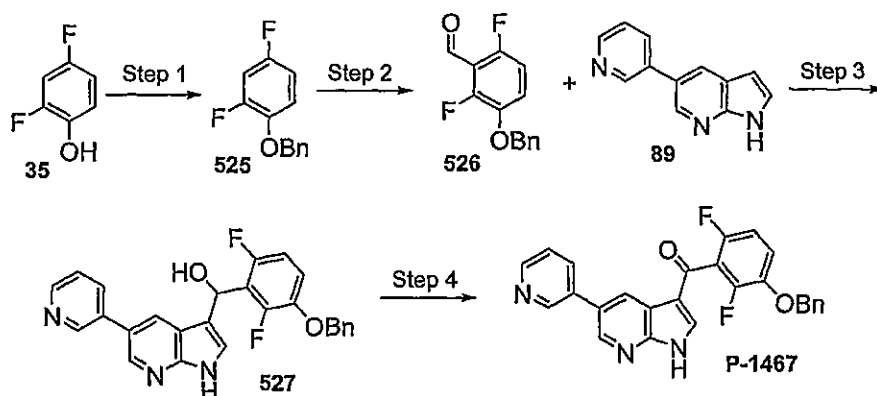
[0313] The corresponding hydroxy-methyl derivative of Scheme 41 Step 2 was reacted following the protocol of Scheme 41a to prepare 4-[5-(2-methoxy-pyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-indole-1-carboxylic acid butylamide **P-1861**, 4-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-indole-1-carboxylic acid butylamide **P-1876**, and 4-(5-Pyridin-4-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-indole-1-carboxylic acid butylamide **P-1877**, with structures shown below.



Example 23: Synthesis of (3-Benzyloxy-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-1467 and related compounds**

[0314] Compound **P-1467** was synthesized in four steps from 2,4-difluorophenol **35** as shown in Scheme 43.

Scheme 43



Step 1 – Preparation of 1-Benzyloxy-2,4-difluoro-benzene (525):

[0315] To 2,4-difluorophenol (**35**, 7.60 g, 0.0584 mol) in N,N-dimethylformamide (50.0 mL) were added benzyl bromide (8.0 mL, 0.067 mol) and potassium carbonate (9.00 g, 0.0651 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% ethyl acetate in hexane to give the compound as white solid (**525**, 3.20 g, 25%).

Step 2 – Preparation of 3-Benzyloxy-2,6-difluoro-benzaldehyde (526):

[0316] To 1-Benzyloxy-2,4-difluoro-benzene (**525**, 3.00 g, 13.6 mmol) in Tetrahydrofuran (48 mL) under an atmosphere of nitrogen and cooled with dry ice/acetone was added n-Butyllithium (1.60 M in hexane, 8.94 mL). After 20 minutes, N,N-dimethylformamide (1.46 mL, 0.0189 mol) was added to the reaction. After another 20 minutes, the flask was stirred at room temperature for 30 minutes. The reaction mixture was poured into water, acidified to pH = 1, 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 30% ethyl acetate in hexane to give the compound as a yellow solid (**526**, 2.5g, 74%).

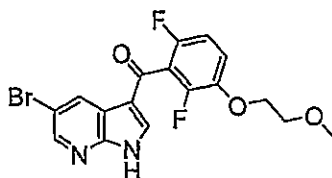
Step 3 – Preparation of (3-Benzyloxy-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (527):

[0317] To 5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**89**, 750.0 mg, 0.003842 mol, prepared as in Example 17) in methanol (20.0 mL) were added 3-Benzyloxy-2,6-difluoro-benzaldehyde (**526**, 1.12 g, 4.5 mmol) and potassium hydroxide (1.50 g, 0.0267 mol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight and then poured into water, acidified with 1N HCl to pH around 2 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 compound (**527**, 700 mg, 35%).

Step 4 – Preparation of (3-Benzyloxy-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1467):

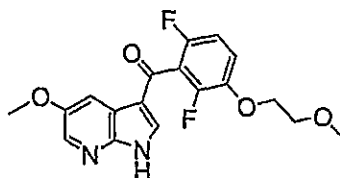
[0318] To (3-Benzyloxy-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**527**, 300.0 mg, 0.68 mmol) in tetrahydrofuran (10.0 mL) was added Dess-Martin periodinane (344 mg, 0.81 mmol). The reaction was stirred at room temperature for 10 minutes. The reaction mixture was concentrated with silica and purified with silica gel column chromatography eluting with 10% methanol in dichloromethane to give the compound (**P-1467**, 240 mg, 80%).
MS(ESI) $[M+H]^+ = 442.2$.

[0319] (5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2,6-difluoro-3-(2-methoxy-ethoxy)-phenyl]-methanone **P-1453**



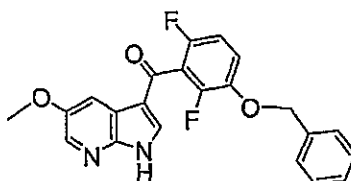
was prepared following the protocol of Scheme 43, substituting benzyl bromide with 1-Bromo-2-methoxy-ethane in Step 1 and 5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine with 5-Bromo-1H-pyrrolo[2,3-b]pyridine (**67**) in Step 3. MS (ESI) $[M + H]^+ = 410.1, 412.1$.

[0320] [2,6-Difluoro-3-(2-methoxy-ethoxy)-phenyl]-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-1584**



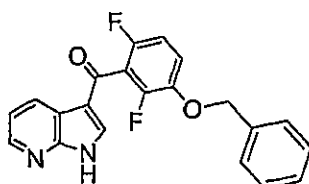
was prepared following the protocol of Scheme 43, substituting benzyl bromide with 1-Bromo-2-methoxy-ethane in Step 1 and 5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine with 5-methoxy-1H-pyrrolo[2,3-b]pyridine (**104**, prepared as in Example 22) in Step 3. MS (ESI) $[M + H]^+ = 363.2$.

[0321] (3-Benzyloxy-2,6-difluoro-phenyl)-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-1597**

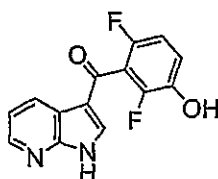


was prepared following the protocol of Scheme 43, substituting 5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine with 5-methoxy-1H-pyrrolo[2,3-b]pyridine (**104**, prepared as in Example 16) in Step 3. MS(ESI) $[M + H]^+ = 395.2$.

[0322] (3-Benzyloxy-2,6-difluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-1802**



was prepared following the protocol of Scheme 43, substituting 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine with 7-azaindole. To a solution of (3-benzyloxy-2,6-difluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-1802**, 0.5 g, 1.37 mol) in methanol (70 mL) and tetrahydrofuran (30 mL) was added palladium on carbon (120 mg, 10% wt., 0.58 mol). The mixture was stirred under hydrogenation (60 psi) for six hours. After removal of solvent, the residue was dried under vacuum, which provided (2,6-Difluoro-3-hydroxy-phenyl)-(1H-pyrrolo[2,3-b]pyridine-3-yl)-methanone **651**



as a white solid (363 mg, 96%). MS (ESI) $[M+H]^+ = 275.36$.

[0323] Additional compounds were prepared following steps 3 and 4 of Scheme 43, replacing 3-benzyloxy-2,6-difluoro-benzaldehyde **526** with an appropriate aldehyde and/or pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** with an appropriate azaindole in Step 3. The azaindoles used were synthesized as described in Examples 9 or 16. The aldehydes used were synthesized as described in Example 5 or 21. The following compounds were made following this procedure:

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1541**),

N-[2,4-Difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-1542**),

N-[2,4-Difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-fluoro-benzenesulfonamide (**P-1581**),

N-[2,4-Difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-fluoro-benzenesulfonamide (**P-1582**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-fluoro-benzenesulfonamide (**P-1583**),

N-[2,4-Difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-trifluoromethyl-benzenesulfonamide (**P-1598**),

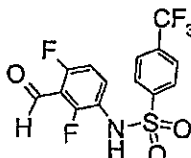
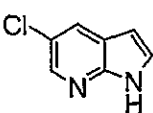
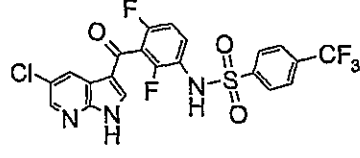
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-trifluoromethyl-benzenesulfonamide (**P-1599**),

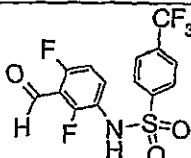
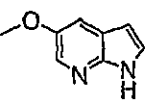
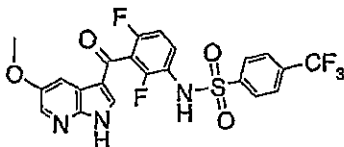
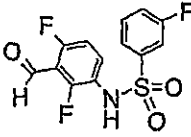
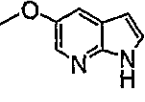
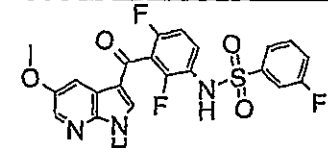
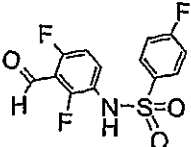
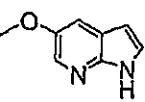
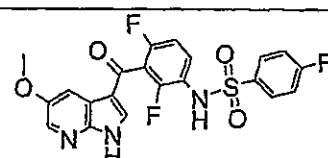
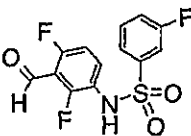
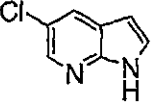
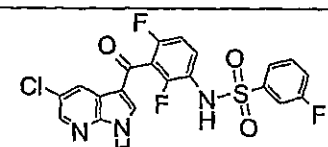
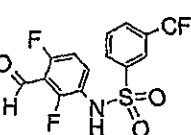
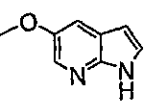
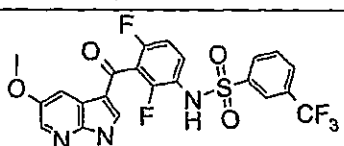
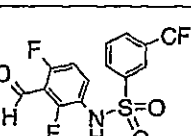
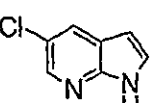
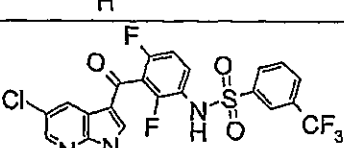
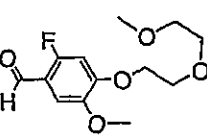
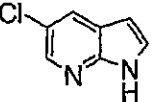
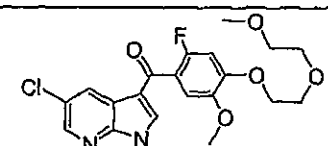
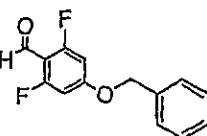
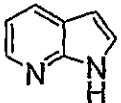
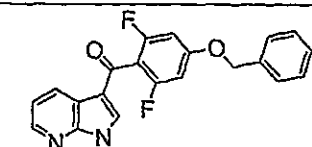
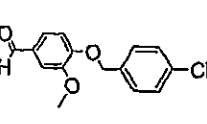
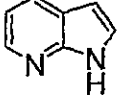
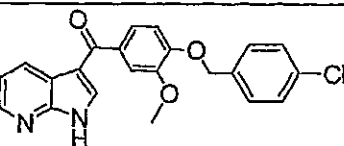
(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-{2-fluoro-5-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-methanone (**P-2003**),

(4-Benzyloxy-2,6-difluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2020**), and

[4-(4-Chloro-benzyloxy)-3-methoxy-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-1698**).

The following table indicates the aldehyde (column 2) and the azaindole (column 3) used to afford the target compound (column 4). Column 1 provides the compound number and column 5 the observed mass.

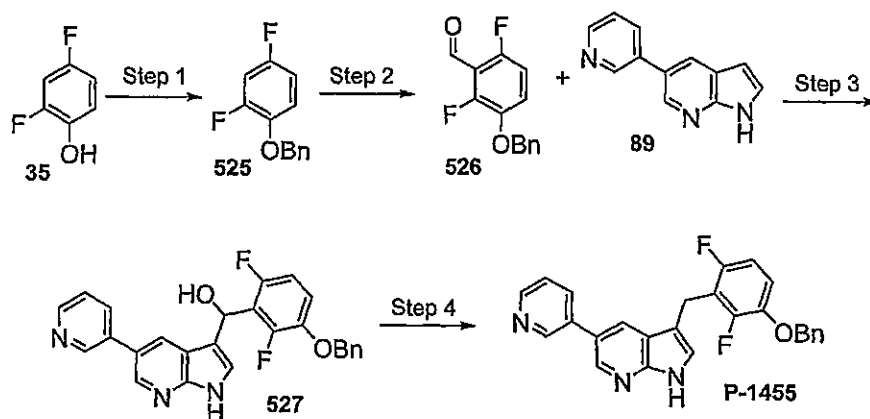
	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1541				516.2

	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1542				512.2
P-1581				462.2
P-1582				462.2
P-1583				466.1
P-1598				510.1
P-1599				514.0
P-2003				423.3
P-2020				363.1
P-1698				393.2

Example 24: Synthesis of 3-(3-Benzyloxy-2,6-difluoro-benzyl)-5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine P-1455:

[0324] Compound P-1455 was synthesized in four steps from 2,4-difluorophenol 35 as shown in Scheme 43a.

Scheme 43a

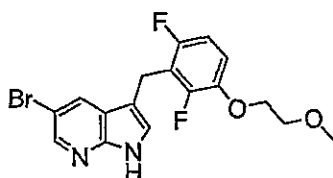


[0325] Steps 1-3 are identical to Steps 1-3 of Scheme 43.

Step 4 – Preparation of 3-(3-Benzyloxy-2,6-difluoro-benzyl) -5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (P-1455):

[0326] To (3-Benzyloxy-2,6-difluoro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (527, 580.0 mg, 1.3 mmol) in acetonitrile (29.0 mL) were added trifluoroacetic acid (1.9 mL, 0.025 mol) and triethylsilane (3.9 mL, 0.024 mol). The reaction was stirred at 80 °C for 1 hour. The reaction was poured into water, basified with 1 M potassium carbonate to pH = 4, 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 50% ethyl acetate in hexane to give as a yellow solid (P-1455, 530 mg). MS(ESI) $[M+H]^+ = 428.3$.

[0327] 5-Bromo-3-[2,6-difluoro-3-(2-methoxy-ethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine P-1454



was prepared following the protocol of Scheme 43a by substituting benzyl bromide with 1-Bromo-2-methoxy-ethane in Step 1 and 5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine with 5-Bromo-1H-pyrrolo[2,3-b]pyridine (67) in Step 3. MS (ESI) $[M+H]^+ = 410.1, 412.1$.

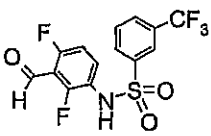
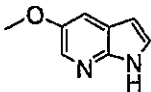
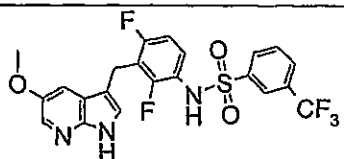
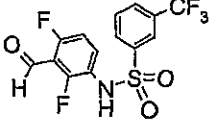
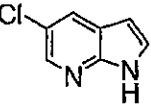
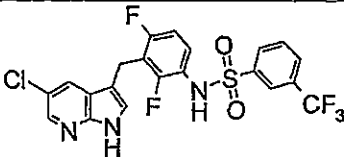
[0328] Additional compounds were prepared following steps 3 and 4 of Scheme 43a, replacing 3-benzyloxy-2,6-difluoro-benzaldehyde **526** with an appropriate aldehyde and/or pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** with an appropriate azaindole (see Example 9 or Example 16) in Step 3.

The following compounds were made following this procedure:

N-[2,4-Difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-3-trifluoromethyl-benzenesulfonamide (**P-1590**), and

N-[2,4-Difluoro-3-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-3-trifluoromethyl-benzenesulfonamide (**P-1600**).

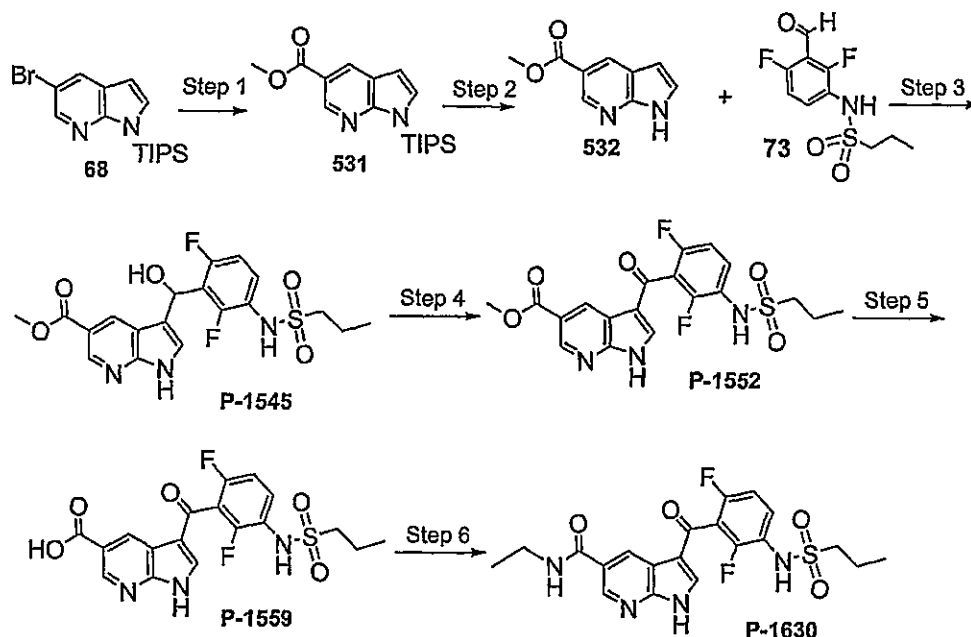
The following table indicates the aldehyde (column 2) and the azaindole (column 3) used to afford the target compound (column 4). Column 1 indicates the compound number and column 5 the observed mass.

	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1590				
P-1600				

Example 25: Synthesis of 3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethylamide **P-1630**

[0329] Compound **P-1630** was synthesized in six steps from 5-bromo-1-triisopropylsilyl-7-azaindole **68** as shown in Scheme 45.

Scheme 45



Step 1 – Preparation of 1-Triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester (531):

[0330] To 5-bromo-1-triisopropylsilyl-7-azaindole (**68**, 1.50 g, 4.2 mmol, prepared as described in Example 6) in tetrahydrofuran (20.0 mL) under an atmosphere of nitrogen, cooled with dry ice/acetone, was slowly added *n*-Butyllithium (10.0 M in hexane, 0.467 mL). After 60 minutes, methyl chloroformate (0.394 mL, 5.1 mmol) was added to the reaction. After another 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 to give the crude compound as a light yellow solid that was used directly in the next step.

Step 2 – Preparation of 1H-Pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester (532):

[0331] To 1-Triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester (**531**, 0.950 g, 2.9 mmol) in tetrahydrofuran (20.0 mL) was added tetrabutyl-ammonium fluoride, trihydrate (1.20 g, 3.8 mmol). The reaction was stirred at room temperature for 10 minutes. The reaction was concentrated and purified with silica gel column chromatography eluting with 4% methanol in methylene chloride to give the compound as a white solid (**532**, 300 mg, 60%). MS(ESI) $[M+H]^+ = 177.2$.

Step 3 – Preparation of 3-[2,6-difluoro-3-(propane-1-sulfonylamino)-phenyl]-hydroxy-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester (P-1545):

[0332] To 1H-Pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester (**532**, 155.0 mg, 0.88 mmol) in methanol (15.0 mL) were added propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (**73**,

260.0 mg, 0.99 mmol, prepared as described in Example 7) and potassium hydroxide (859 mg, 15.3 mmol) 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% ethyl acetate in hexane to give the compound as white solid (**P-1545**, 110 mg, 28%). MS(ESI) $[M+H]^+ = 440.2$.

*Step 4 – Preparation of 3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester (**P-1552**):*

[0333] To 3-[2,6-difluoro-3-(propane-1-sulfonylamino)-phenyl]-hydroxy-methyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester (**P-1545**, 100.0 mg, 0.23 mmol) in tetrahydrofuran (10 mL) was added Dess-Martin periodinane (107 mg, 2.5 mmol). The reaction was stirred at room temperature for 10 minutes. The reaction mixture was concentrated with silica gel and then purified with silica gel column chromatography eluting with 30% ethyl acetate in hexane to give the compound as white solid (**P-1552**, 80 mg, 80%). MS(ESI) $[M+H]^+ = 438.2$.

*Step 5 – Preparation of 3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid (**P-1559**):*

[0334] To 3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester (**P-1552**, 80.0 mg, 0.18 mmol) in tetrahydrofuran (10.0 mL) were added water (3.0 mL) and lithium hydroxide (82 mg, 3.4 mmol). The reaction was stirred at room temperature overnight. The reaction was poured into water, acidified with 1 N HCl to pH around 1, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated, and washed with ethyl acetate to give an off-white solid (**P-1559**, 60 mg, 77%) MS(ESI) $[M+H]^+ = 424.2$.

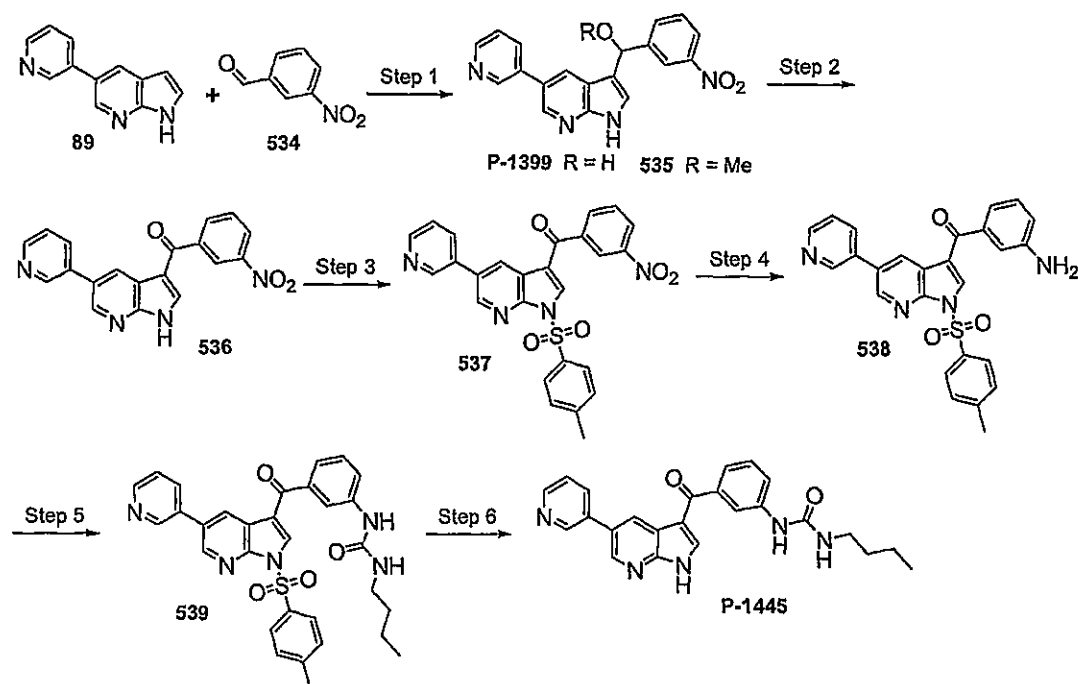
*Step 6: Preparation of 3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethylamide (**P-1630**):*

[0335] To 3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid (**P-1559**, 38.0 mg, 0.090 mmol) in tetrahydrofuran (2.3 mL) was added a solution of ethylamine (2.0 M in tetrahydrofuran, 0.20 mL), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (80.0 mg, 0.17 mmol) and triethylamine (0.30 mL, 2.2 mmol) under an atmosphere of nitrogen. The reaction mixture was stirred overnight at room temperature. 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 the compound as a white solid (**P-1630**, 13.2 mg, 33%). MS(ESI) $[M-H]^+ = 449.0$.

Example 26: Synthesis of 1-butyl-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-urea P-1445.

[0336] Compound P-1445 was synthesized in six steps from 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** as shown in Scheme 49.

Scheme 49



Step 1 – Preparation of (3-nitro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (P-1399):

[0337] To 3-nitrobenzaldehyde (**534**, 1.08 g, 7.17 mmol) in methanol (34 mL) was added 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**89**, 1.08 g, 5.52 mmol, prepared as described in Example 17) and potassium hydroxide (1.55 g, 27.6 mmol). The reaction was stirred at room temperature for four hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The mixture was purified by silica gel column chromatography eluting with 4% methanol in dichloromethane to provide two different compounds, a white solid (P-1399, R=H, 1.20 g, 63%) MS(ESI) $[M+H]^+ = 347.2$, and a light yellow solid (535, R=Me, 0.434 g, 22%).

Step 2 – Preparation of (3-nitro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (536):

[0338] To (3-nitro-phenyl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (P-1399, R=H, 500 mg, 1.44 mmol) in dimethylformamide (26 mL) was added Dess-Martin periodane (674

mg, 1.59 mmol). The reaction was stirred for one hour and the reaction was poured into water. All solids were filtered and purified by silica gel column chromatography eluting with 3 % methanol in dichloromethane to give the compound (536, 295 mg, 59 %). MS(ESI)[M+H]⁺ = 345.2.

Step 3 – Preparation of (3-nitro-phenyl)-[5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methanone (537):

[0339] To (3-nitro-phenyl)-[5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl]-methanone (536, 291 mg, 0.85 mmol) in tetrahydrofuran (7 mL) was added 1.5 M of lithium diisopropylamide in cyclohexane (676 µl, 1.59 mmol) at -78 °C under an atmosphere of nitrogen. After 30 minutes, p-toluenesulfonyl chloride (209 mg, 1.10 mmol) was added in tetrahydrofuran and the reaction was stirred for three hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. All solids were filtered and purified by silica gel column chromatography eluting with 60 % ethyl acetate in hexane to give the compound (537, 182 mg, 43 %). MS(ESI)[M+H]⁺ = 499.2.

Step 4 – Preparation of (3-Amino-phenyl)-[5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methanone (538):

[0340] To (3-nitro-phenyl)-[5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methanone (537, 180 mg, 0.361 mmol) in methanol (4 mL) was added 10% palladium on carbon (20 mg) and few drops of concentrated aqueous hydrochloric acid. The resulting mixture was stirred under an atmosphere of hydrogen overnight and the catalyst was filtered out through a bed of celite. The filtrate was concentrated and purified by silica gel column chromatography eluting with 90 % ethyl acetate in hexane to give the compound (538, 58 mg, 34 %). MS(ESI)[M+H]⁺ = 469.3.

Step 5 – Preparation of 1-Butyl-3-3-[5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl-urea (539):

[0341] To (3-Amino-phenyl)-[5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methanone (538, 53 mg, 0.11 mmol) in tetrahydrofuran (1.6 mL) was added 1-isocyanatobutane (12 mg, 0.12 mmol). The reaction was heated at 90 °C overnight and it was concentrated and purified by silica gel column chromatography eluting with 2 % methanol in dichloromethane to give the compound (539, 39 mg, 61%). MS(ESI)[M+H]⁺ = 568.4.

Step 6 – Preparation of 1-Butyl-3-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1445):

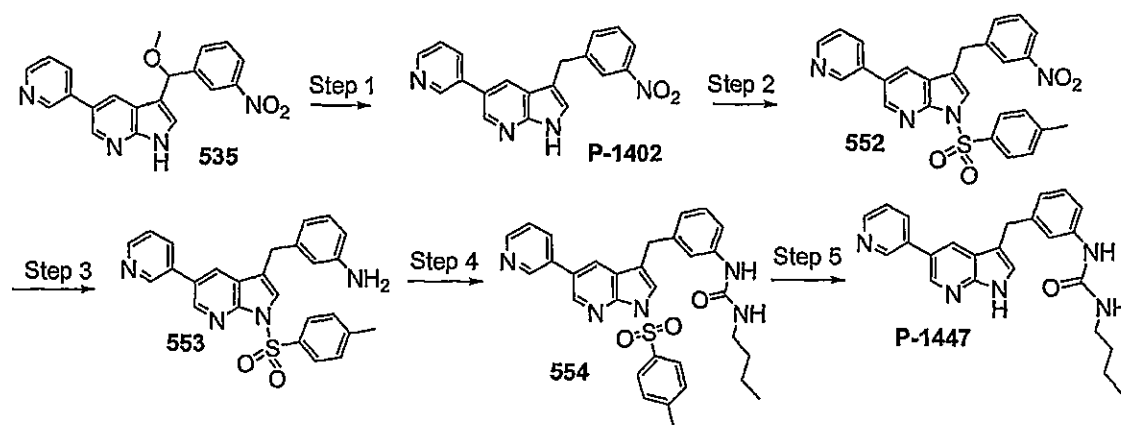
[0342] To 1-Butyl-3-3-[5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl-urea (539, 33 mg, 0.058 mmol) in tetrahydrofuran (2 mL) was added 1.0 M tetra-n-butylammonium fluoride in tetrahydrofuran (192 µl) under an atmosphere of nitrogen and the reaction was stirred for three hours. The reaction was poured into water and extracted with ethyl acetate. The

organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. All solids were filtered and purified by silica gel column chromatography eluting with 4 % methanol in dichloromethane to give the compound (**P-1445**, 8 mg, 30 %). MS(ESI)[M+H]⁺ = 414.3.

Example 27: Synthesis of 1-butyl-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-urea **P-1447**

[0343] Compound **P-1447** was synthesized in five steps from 3-[(3-nitro-phenyl)-methoxy-methyl]-5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **535** as shown in Scheme 50.

Scheme 50



*Step 1 – Preparation of 3-(3-nitro-benzyl)-5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**P-1402**):*

[0344] To 3-[(3-nitro-phenyl)-methoxy-methyl]-5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**535**, 431 mg, 1.20 mmol, per Example 26, Scheme 49 Step 1) in acetonitrile (130 mL), were added trifluoroacetic acid (18 mL, 230 mmol) and triethylsilane (36 mL, 230 mmol). The reaction was refluxed for three hours. The reaction mixture was poured into sodium bicarbonate solution 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 80% ethyl acetate in hexane to give the compound (**P-1402**, 323 mg, 82%).

MS(ESI)[M+H]⁺ = 331.2.

*Step 2 – Preparation of 3-(3-nitro-benzyl)-5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (**552**):*

[0345] To 3-(3-nitro-benzyl)-5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**P-1402**, 141 mg, 0.43 mmol) in N,N-dimethylformamide (3 mL) was added sodium hydride (60% dispersion in mineral oil, 21 mg, 0.512 mmol) under an atmosphere of nitrogen. After thirty minutes, p-toluenesulfonyl chloride (114 mg, 0.60 mmol) in N,N-dimethyl-formamide was added and the reaction was stirred for three hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. All solids were

filtered and purified by silica gel column chromatography eluting with 40 % ethyl acetate in hexane to give the compound (**552**, 120 mg, 58 %). MS(ESI)[M+H]⁺ = 485.25.

Step 3 – Preparation of 3-[5-Pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-phenylamine (553):

[0346] To 3-(3-nitro-benzyl)-5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (**552**, 230 mg, 0.14 mmol) in methanol (5 mL) was added 10% palladium on carbon (10 mg) and few drops of concentrated aqueous hydrochloric acid. The resulting mixture was stirred under an atmosphere of hydrogen overnight, and the catalyst was filtered out through a bed of celite. The filtrate was concentrated and purified by silica gel column chromatography eluting with 90 % ethyl acetate in hexane to give the compound (**553**, 88 mg, 41 %). MS(ESI)[M+H]⁺ = 455.3.

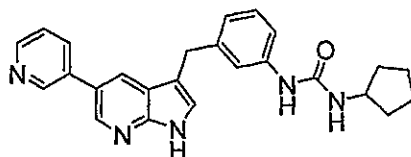
Step 4 – Preparation of 1-butyl-3-3-[5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-phenyl-urea (554):

[0347] To 3-[5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-phenylamine (**553**, 14 mg, 0.031 mmol) in tetrahydrofuran (0.5 mL) was added 1-isocyanatobutane (3.4 mg, 0.03 mmol). The reaction was heated at 90 °C overnight and was concentrated and purified by silica gel column chromatography eluting with 2 % methanol in dichloromethane to give the compound (**554**, 7.2 mg, 42 %). MS(ESI)[M+H]⁺ = 554.4.

Step 5 – Preparation of 1-Butyl-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-urea (P-1447):

[0348] To 1-butyl-3-3-[5-pyridin-3-yl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-phenyl-urea (**554**, 11 mg, 0.02 mmol) in tetrahydrofuran (0.7 mL) was added 1.0 M tetra-n-butylammonium fluoride in tetrahydrofuran (66 µL) under an atmosphere of nitrogen and the reaction was stirred for three hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. All solids were filtered and purified by silica gel column chromatography eluting with 4 % methanol in dichloromethane to give the compound (**P-1447**, 2.5 mg, 31 %). MS(ESI)[M+H]⁺ = 400.3.

[0349] 1-Cyclopentyl-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-urea **P-1446**

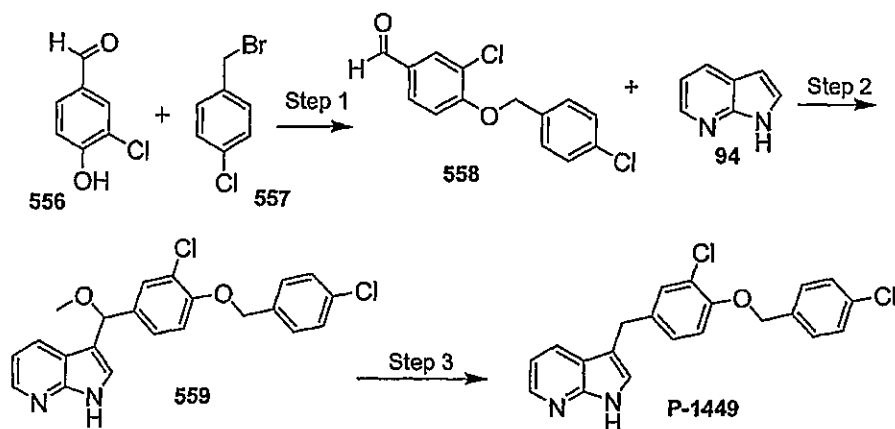


was prepared following the protocol of Scheme 50, substituting 1-isocyanatobutane with isocyanatocyclopentane in Step 4. MS(ESI) [M + H]⁺ = 412.4.

Example 28: Synthesis of 3-[3-chloro-4-(4-chloro-benzyloxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine P-1449.

[0350] Compound P-1449 was synthesized in three steps from 3-chloro-4-hydroxy-benzaldehyde 556 as shown in Scheme 51.

Scheme 51



Step 1 – Preparation of 3-chloro-4-(4-chloro-benzyloxy)-benzaldehyde (558):

[0351] To acetonitrile (15.0 mL) were added 3-chloro-4-hydroxy-benzaldehyde (556, 0.6 g, 4 mmol), 4-chlorobenzyl bromide (557, 1.2 g, 6 mmol), and potassium carbonate (0.9 g, 7 mmol). The reaction was heated to 150 °C for 10 minutes in a CEM Discover microwave instrument. The reaction was poured into water, extracted with ethyl acetate, and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The desired compound was isolated by silica gel column chromatography (ethyl acetate: hexanes) (558, 0.85 g, 76%).

Step 2 – Preparation of 3-[3-chloro-4-(4-chloro-benzyloxy)-phenyl]-methoxy-methyl-1H-pyrrolo[2,3-b]pyridine (559):

[0352] 1H-Pyrrolo[2,3-b]pyridine (94, 0.3 g, 2.8 mmol) was mixed with 3-chloro-4-(4-chloro-benzyloxy)-benzaldehyde (558, 0.8 g, 3 mmol), potassium hydroxide (0.9 g, 17 mmol) and methanol (90.0 mL). The reaction was heated to 50 °C under an atmosphere of nitrogen for six days. After neutralization with 6N hydrochloric acid the reaction was poured into water, extracted with ethyl acetate, and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The desired compound was isolated by silica gel column chromatography (ethyl acetate: hexanes) to give a yellow solid (559, 0.6 g, 41%). MS(ESI) $[M + H]^+ = 413.2, 415.2$ $[M - H]^+ = 411.1, 413.1$.

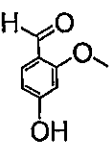
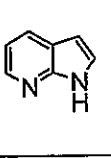
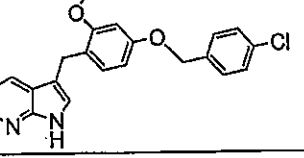
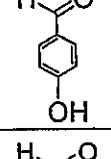
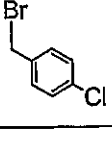
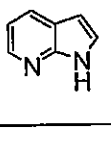
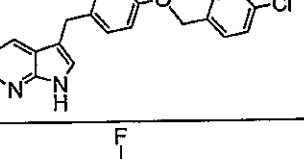
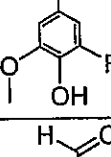
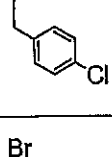
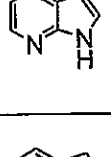
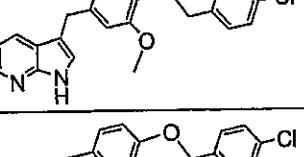
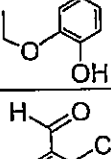
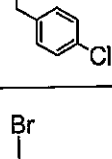
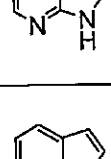
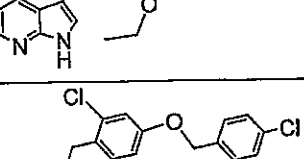
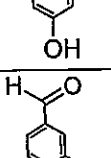
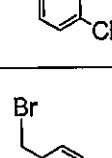
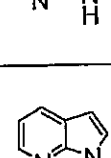
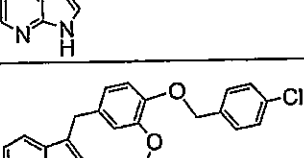
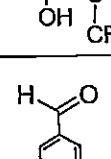
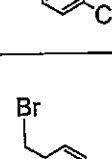
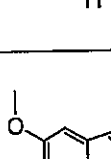
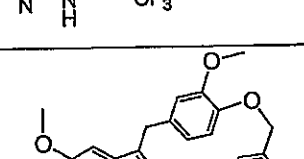
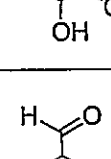
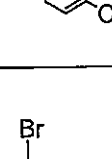
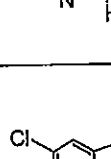
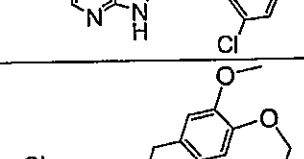
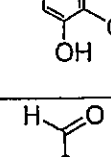
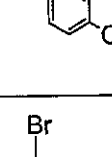
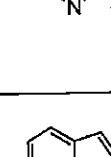
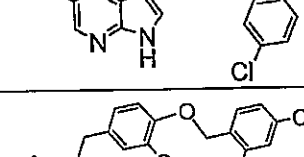
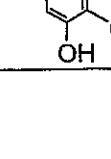
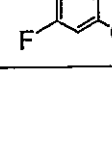
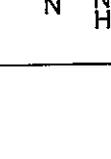
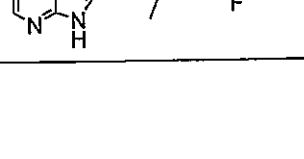
Step 3 – Preparation of 3-[3-chloro-4-(4-chloro-benzyloxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1449):

[0353] 3-[3-Chloro-4-(4-chloro-benzyloxy)-phenyl]-methoxy-methyl-1H-pyrrolo[2,3-b]pyridine (559, 0.2 g, 0.6 mmol) was mixed with trifluoroacetic acid (0.226 mL, 3 mmol), triethylsilane (0.4 mL, 3 mmol) and acetonitrile (5 mL). The reaction was heated at 50 °C and stirred for two days. The reaction was concentrated. The residue was diluted with ethyl acetate and neutralized with 2M aqueous sodium hydroxide. The reaction was poured into water, extracted with ethyl acetate, and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The desired compound was isolated by silica gel column chromatography (ethyl acetate: hexanes) to give a yellow solid (P-1449, 0.0744 g, 33%). MS(ESI) $[M + H]^+ = 383.2, 385.2$.

[0354] Additional compounds were prepared following the protocol of Scheme 51, replacing 3-chloro-4-hydroxy-benzaldehyde 556 with an appropriate aldehyde and optionally replacing 4-chlorobenzyl bromide 557 with an appropriate benzyl halide in Step 1, and optionally replacing 1H-pyrrolo[2,3-b]pyridine 94 with an appropriate azaindole in Step 2. The following compounds were made following this procedure:

3-[4-(4-chloro-benzyloxy)-2-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1450),
 3-[4-(4-Chloro-benzyloxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1462),
 3-[4-(4-Chloro-benzyloxy)-3-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1466),
 3-[4-(4-Chloro-benzyloxy)-3-ethoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1470),
 3-[2-Chloro-4-(4-chloro-benzyloxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1471),
 3-[4-(4-Chloro-benzyloxy)-3-trifluoromethoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1487),
 3-[4-(4-Chloro-benzyloxy)-3-methoxy-benzyl]-5-methoxy-1H-pyrrolo[2,3-b]pyridine (P-1531),
 5-Chloro-3-[4-(4-chloro-benzyloxy)-3-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1532),
 3-[4-(4-Chloro-2-fluoro-benzyloxy)-3-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1544),
 3-[4-(2,4-Dichloro-benzyloxy)-3-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1568),
 3-[3-Methoxy-4-(4-methoxy-benzyloxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1569),
 3-[3-Methoxy-4-(2,4,6-trifluoro-benzyloxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1578),
 3-[4-(2,6-Dichloro-benzyloxy)-3-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1579), and 3-[3-Chloro-4-(4-chloro-benzyloxy)-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1616).

The following table indicates the aldehyde (column 2), the benzyl halide (column 3), and the azaindole (column 4) used to afford the target compound (column 5). Column 1 indicates the compound number and column 6 the observed mass.

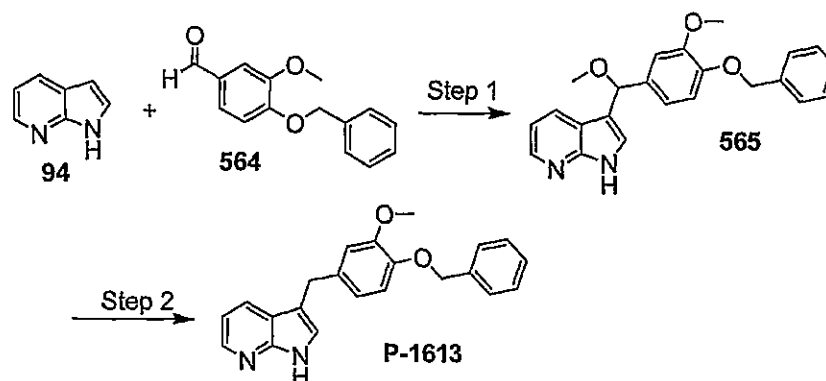
	Aldehyde	Benzyl halide	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1450					379.2 381.2
P-1462					349.1 351.2
P-1466					397.2 399.2
P-1470					393.2 395.2
P-1471					383.1 385.1
P-1487					433.2 435.2
P-1531					409.2
P-1532					413.1
P-1544					397.2

	Aldehyde	Benzyl halide	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1568					413.1 415.1 416.2
P-1569					375.2
P-1578					399.2 397.1 ([M-H] ⁺)
P-1579					413.2 415.2 416.2 ([M-H] ⁺)
P-1616					413.1

Example 29: Synthesis of 3-(4-benzyloxy-3-methoxy-benzyl)-1H-pyrrolo[2,3-b]pyridine P-1613.

[0355] Compound P-1613 was synthesized in two steps from 4-benzyloxy-3-methoxybenzaldehyde 564 as shown in Scheme 53.

Scheme 53



Step 1 – Preparation of 3-[(4-benzyloxy-3-methoxy-phenyl)-methoxy-methyl]-1H-pyrrolo[2,3-b]pyridine (565):

[0356] Methanol (125 mL) and potassium hydroxide (4.4 g, 79 mmol) were mixed with 1H-pyrrolo[2,3-b]pyridine (94, 3.1 g, 26.6 mmol) and 4-benzyloxy-3-methoxy-benzaldehyde (564, 12.9 g, 53.2 mmol). The reaction was stirred at room temperature for 2 days. The resulting white solid was filtered and washed with water. Crude material was carried forward without further purification.

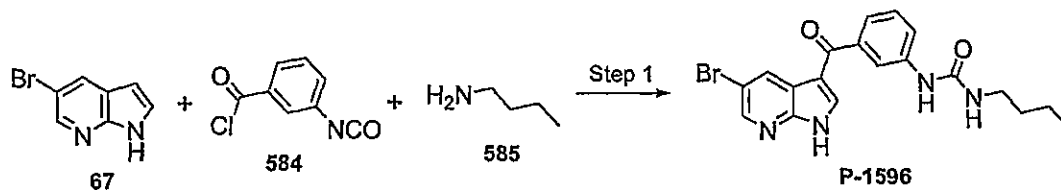
Step 2 – Preparation of 3-(4-benzyloxy-3-methoxy-benzyl)-1H-pyrrolo[2,3-b]pyridine (P-1613):

[0357] 3-[(4-Benzyloxy-3-methoxy-phenyl)-methoxy-methyl]-1H-pyrrolo[2,3-b]pyridine (565, 0.9g, 2.4 mmol) and acetonitrile (50 mL) were mixed with trifluoroacetic acid (0.360 mL, 4.7 mmol) and triethylsilane (0.746 mL, 4.7 mmol). The reaction was heated at 80 °C and stirred overnight. The reaction was concentrated. The mixture was extracted with ethyl acetate and saturated sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The desired compound was isolated by silica gel column chromatography to give the compound (P-1613, 0.454 g 54.8%). MS(ESI) $[M + H]^+ = 345.3$.

Example 30: Synthesis of 1-[3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-butyl-urea P-1596.

[0358] Compound P-1596 was synthesized in one step from 5-bromo-1H-pyrrolo[2,3-b]pyridine 67 as shown in Scheme 55.

Scheme 55



Step 1 – Preparation of 1-[3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-butyl-urea (P-1596):

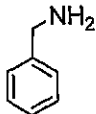
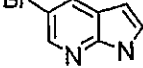
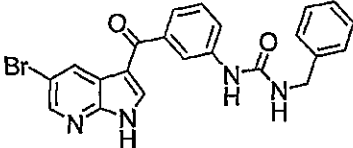
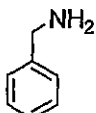
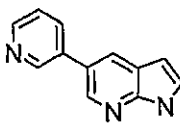
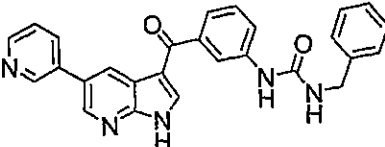
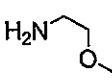
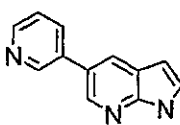
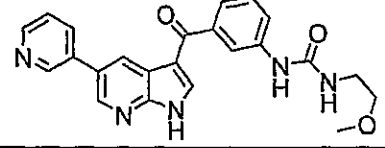
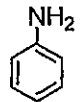
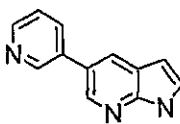
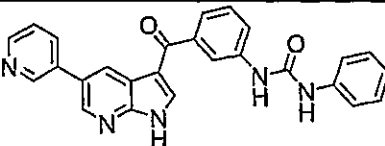
[0359] To aluminum trichloride (3.67 g, 0.0275 mol) in dichloromethane (100 mL, 2 mol) under an atmosphere of nitrogen was added 5-bromo-7-azaindole (67, 1.08 g, 0.00548 mol) at room temperature. After one hour, 3-isocyanato-benzoyl chloride (584, 5.00 g, 0.0275 mol) was added under an atmosphere of nitrogen at room temperature. The resulting mixture was stirred over night at room temperature. 1-Butanamine (585, 54 mL, 0.54 mol) was added carefully. All solvents were removed. The residue was purified by silica gel column chromatography to give the compound (P-1596, 172 mg, 8%). MS(ESI) $[M-H]^- = 413.1, 415.0$.

[0360] Additional compounds were prepared following the protocol of Scheme 55, replacing 1-butanamine **585** with an appropriate amine and optionally replacing 5-bromo-7-azaindole **67** with 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** (prepared as described in Example 17). The following compounds were made following this procedure:

1-Benzyl-3-[3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1553**),
 1-Benzyl-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1554**),
 1-(2-Methoxy-ethyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1566**), and

1-Phenyl-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1591**).

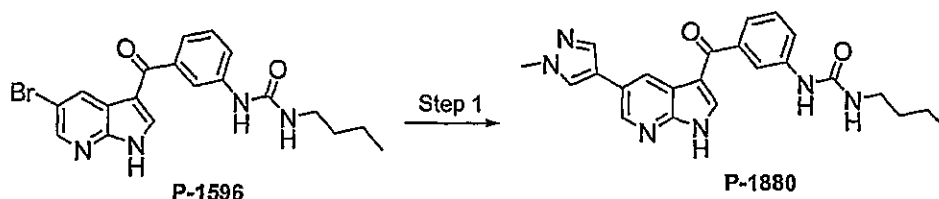
The following table indicates the amine (column 2) and the azaindole (column 3) used to afford the target compound (column 4). The compound number is provided in column 1 and the observed mass in column 5.

	Amine	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1553				447.0 449.1
P-1554				448.3
P-1566				416.3
P-1591				434.3

Example 31: Synthesis of 1-Butyl-3-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl-urea P-1880

[0361] Compound **P-1880** was synthesized in one step from 1-[3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-butyl-urea **P-1596** as shown in Scheme 56.

Scheme 56



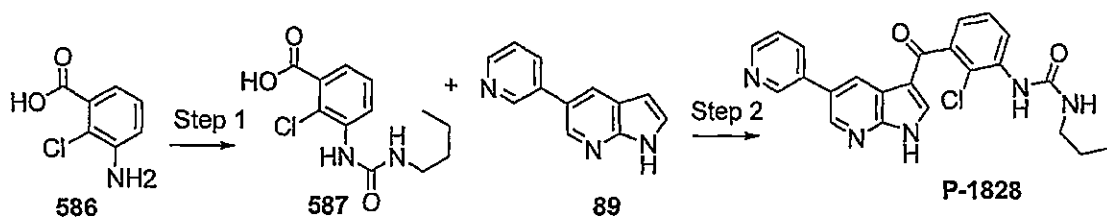
Step 1 – Preparation of 1-Butyl-3-[3-(1-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-butyl-urea (P-1880):

[0362] In a microwave tube, 1-[3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-butyl-urea (P-1596, 0.077 g, 0.00018 mol, prepared as described in Example 47), 1-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (0.0964 g, 0.000464 mol), and Tetrakis(triphenylphosphine)palladium(0) (0.011 g, 0.0000093 mol) were mixed in 1.00 M of potassium carbonate in water (1.2 mL), acetonitrile (2.0 mL, 0.037 mol), and tetrahydrofuran (1.0 mL, 0.012 mol). The resulting mixture was heated at 100 °C in the microwave for 20 minutes, then at 120 °C for 10 minutes. 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 to give the compound (P-1880, 52 mg, 67%). MS(ESI)[M+H]⁺ = 417.4.

Example 32: Synthesis of 1-Butyl-3-[2-chloro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea P-1828

[0363] Compound P-1828 was synthesized in two steps from 3-amino-2-chlorobenzoic acid 586 as shown in Scheme 57.

Scheme 57



Step 1 – Preparation of (3-Butyl-ureido)-2-chloro-benzoic acid (587):

[0364] To N,N-diisopropylamine (1.72 mL, 0.0122 mol) in tetrahydrofuran (12 mL, 0.14 mol), was added 1.6 M n-butyllithium in hexane (7.6 mL) at -78 °C under an atmosphere of nitrogen. After 30 minutes, 3-amino-2-chlorobenzoic acid (586, 1.00 g, 0.00583 mol) was added. After another 30 minutes, 1-isocyanatobutane (2.60 mL, 0.0233 mol) was added at -78 °C under an atmosphere of nitrogen and allowed to stir for two hours. The reaction mixture was warmed up to room temperature

and stirred at room temperature for 30 minutes. The reaction was quenched with 1M HCl (aqueous) solution and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with dichloromethane:methanol:acetic acid 40:2:1 to give the compound as an off-white solid (**587**, 147 mg, 9%).

Step 2 – Preparation of 1-Butyl-3-[2-chloro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1828):

[0365] To 3-(3-Butyl-ureido)-2-chloro-benzoic acid (**587**, 103 mg, 0.000380 mol) was added dichloromethane (10 mL, 0.2 mol) followed by thionyl chloride (110 μ L, 0.0015 mol) and 1 drop of dimethylformamide to give a suspension. The reaction was stirred at room temperature for 2 hours. Solid material was still present in the reaction mixture, so tetrahydrofuran (0.5 mL, 0.006 mol) was added and continued stirring at room temperature. The reaction became a clear solution after 2 hours, then stirred for another hour. All volatiles were removed under vacuum and the residue stripped from toluene, twice. The solid was then dried under high vacuum for 60 minutes and dissolved in dichloromethane (5 mL). This was added to 5-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (**89**, 0.074 g, 0.00038 mol, prepared as described in Example 17) which had been treated with aluminum trichloride (0.25 g, 0.0019 mol) in dichloromethane (10 mL) for 1 hour. The reaction was stirred at room temperature overnight, then quenched with methanol (5 mL). The resulting solution was extracted with ethyl acetate and water with added saturated sodium bicarbonate to adjust pH $\sim$ 8. The organic layer was washed with sodium bicarbonate and brine and dried over magnesium sulfate and filtered. The organic layer was concentrated and purified by silica gel column chromatography eluting with 2% methanol in dichloromethane followed by 5% methanol in dichloromethane to give the compound as a white solid (**P-1828**, 45 mg, 26%). MS(ESI) $[M+H]^+ = 448.3$.

[0366] Additional compounds were prepared following the protocol of Scheme 57, replacing 3-amino-2-chlorobenzoic acid **586** with an appropriate carboxylic acid and optionally replacing 1-isocyanatobutane with an appropriate isocyanate in Step 1 and optionally replacing 5-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine **89** with an appropriate substituted 7-azaindole (see Example 17) in Step 2. The following compounds were made following this procedure:

1-Butyl-3-[2-methyl-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1742**),

3-Butyl-1-methyl-1-[2-methyl-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1855**),

[3-(5-Bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-fluoro-phenyl]-urea (**P-1570**),

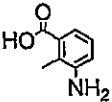
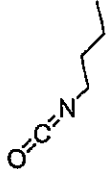
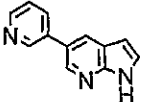
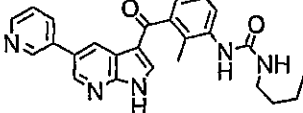
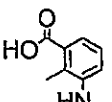
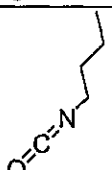
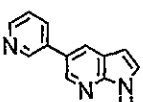
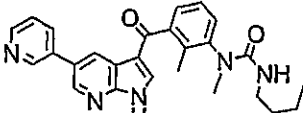
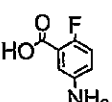
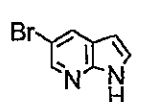
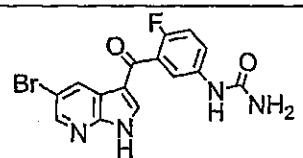
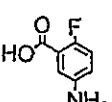
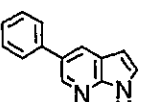
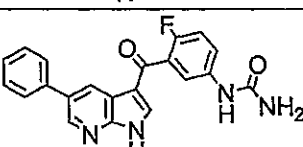
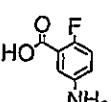
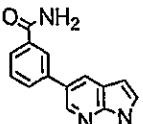
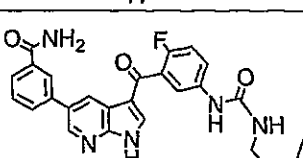
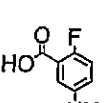
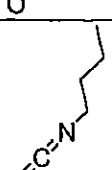
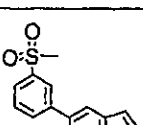
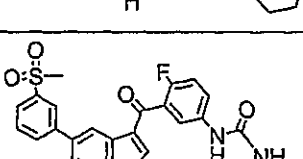
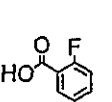
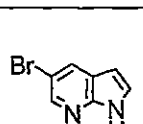
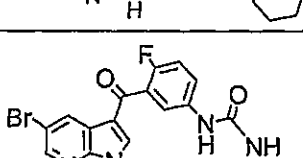
[4-Fluoro-3-(5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (**P-1589**),

3-{3-[5-(3-Butyl-ureido)-2-fluoro-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-benzamide (**P-1621**),

1-Butyl-3-{4-fluoro-3-[5-(3-methane sulfonyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea (**P-1627**), and

1-[3-(5-Bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-fluoro-phenyl]-3-butyl-urea (**P-1637**).

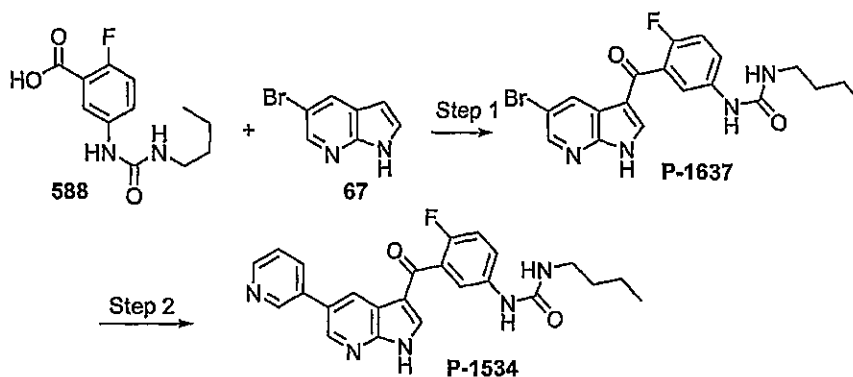
The following table indicates the carboxylic acid (column 2), the isocyanate (column 3), and the azaindole (column 4) used to afford the target compound (column 5). Column 1 indicates the compound number and column 6 the observed mass.

	Acid	Iso-cyanate	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1742					428.3
P-1855					442.3
P-1570		HN=C=O			377.1 379.1
P-1589		HN=C=O			375.2
P-1621					474.3
P-1627					509.2
P-1637					433.1 435.1

Example 33: Synthesis of 1-Butyl-3-[4-fluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1534):

[0367] Compound P-1534 was synthesized in two steps from 5-(3-butylureido)-2-fluorobenzoic acid **588** (prepared from 3-fluoro-5-aminobenzoic acid and 1-isocyanatobutane following the protocol described in Step 1 of Scheme 57, Example 32) and 5-bromo-7-azaindole **67** as shown in Scheme 58.

Scheme 58



Step 1 – Preparation of 1-[3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-fluoro-phenyl]-3-butyl-urea (P-1637):

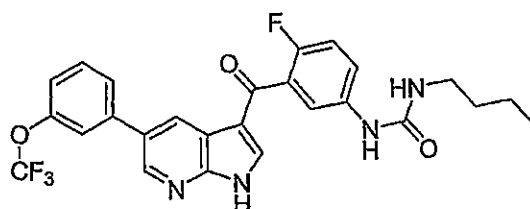
[0368] To aluminum trichloride (0.524 g, 0.00393 mol) and dichloromethane (20 mL, 0.3 mol) under an atmosphere of nitrogen was added 5-bromo-7-azaindole (**67**, 0.155 g, 0.000787 mol) in dichloromethane. To 5-(3-butylureido)-2-fluorobenzoic acid (**588**, 0.200 g, 0.000787 mol) was added 4 mL of dichloromethane (4 mL) followed by thionyl chloride (69 μ L, 0.00094 mol) and a drop of N,N-dimethylformamide. After 1 hour, the reaction remained a suspension so additional thionyl chloride was added along with tetrahydrofuran. The reaction remained a suspension, so was placed in a 50 °C oil bath. After another hour, the reaction was still a suspension, and so was left to react at 50 °C overnight. The reaction had become a clear solution. All volatiles were removed under vacuum, then the residue dissolved in dichloromethane and added to the 5-bromo-7-azaindole and aluminum trichloride suspension. The reaction was allowed to stir at room temperature for 4.5 hours, followed by the addition of water and extraction with ethyl acetate. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with a gradient of methanol (0 to 10%) in dichloromethane to give the compound (**P-1637**, 14 mg, 4%).

Step 2 – Preparation of 1-Butyl-3-[4-fluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1534):

[0369] To 1-[3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-fluoro-phenyl]-3-butyl-urea (**P-1637**, 14.0 mg, 0.0000323 mol), 3-pyridylboronic acid (5.96 mg, 0.0000485 mol), and

Tetrakis(triphenylphosphine)palladium(0) (0.820 mg, 7.09E-7 mol) were mixed in 1.00 M potassium carbonate in water (1.00 mL) and acetonitrile (2.00 mL, 0.0383 mol). The resulting mixture was heated at 120 °C in the microwave for 40 minutes. The reaction was extracted with ethyl acetate and water twice, and the combined organic layers were washed with 1M sodium bicarbonate followed by brine and the organic layer was dried over magnesium sulfate and filtered. The organic layer was concentrated and purified by reverse phase HPLC (acetonitrile and water with 0.1% formic acid) to give the compound as a white solid (P-1637, 8.5 mg, 61%). MS(ESI) $[M+H]^+ = 432.3$.

[0370] 1-Butyl-3-{4-fluoro-3-[5-(3-trifluoromethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea P-1660

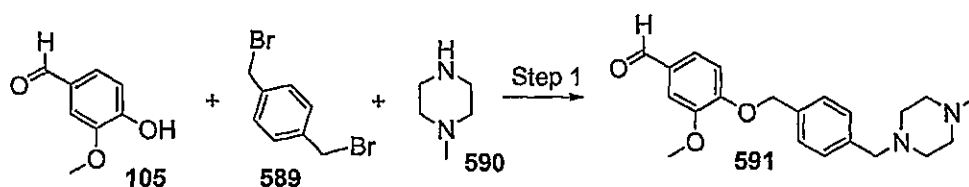


was prepared following the protocol of Scheme 58, replacing 3-Pyridylboronic acid with 3-trifluoromethoxy-phenylboronic acid in Step 2. MS(ESI) $[M+H]^+ = 515.2$.

Example 34: Synthesis of aldehyde reagents for coupling to 7-azaindoles

[0371] Aldehyde compounds for coupling to the 3-position of a 7-azaindole are shown in the following Schemes. 3-Methoxy-4-[4-(4-methyl-piperazin-1-ylmethyl)-benzyloxy]-benzaldehyde **591** was prepared in one Step as shown in Scheme 59.

Scheme 59



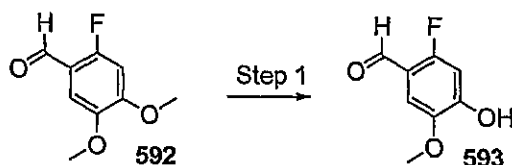
Step 1- Synthesis of 3-Methoxy-4-[4-(4-methyl-piperazin-1-ylmethyl)-benzyloxy]-benzaldehyde (591):

[0372] To 4-Hydroxy-3-methoxybenzaldehyde (**105**, 2.1 g, 0.014 mol) in N,N-dimethylformamide (40.0 mL) were added 1,4-bis(bromomethyl)-benzene (**589**, 4.00 g, 0.0152 mol) and potassium carbonate (5.0 g, 0.036 mol) under an atmosphere of nitrogen. After 12 hours 1-methyl-piperazine (**590**, 3.8 mL, 0.034 mol) was added to the reaction. After 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

20% methanol in dichloromethane to give the compound (**589**, 1.2 g, 25.0%). MS(ESI) $[M+H]^+ = 355.3$.

[0373] 2-Fluoro-4-hydroxy-5-methoxy-benzaldehyde **593** was synthesized in one step from 2-fluoro-4,5-dimethoxy-benzaldehyde **592** as shown in Scheme 60.

Scheme 60

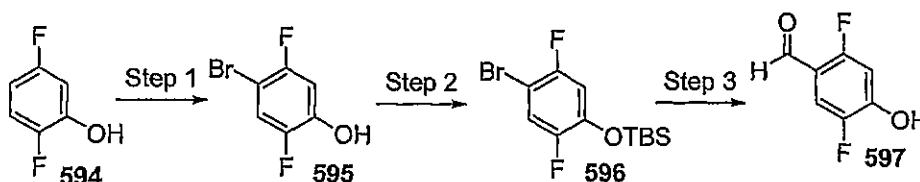


Step 1 – Synthesis of 2-fluoro-4-hydroxy-5-methoxy-benzaldehyde (593):

[0374] To 2-fluoro-4,5-dimethoxy-benzaldehyde (**592**, 1.00 g, 5.43 mol) in dichloromethane (50.0 mL) was added aluminum trichloride (4.34 g, 32.6 mmol) 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 washed with ethyl acetate and hexane to give a white solid (**593**, 0.70g, 76.0%).

[0375] 2,5-Difluoro-4-hydroxy-benzaldehyde **597** was synthesized in three steps from 2,5-difluorophenol **594** as shown in Scheme 61.

Scheme 61



Step 1 – Synthesis of 4-bromo-2,5-difluoro-phenol (595):

[0376] To 2,5-difluorophenol (**594**, 5.50 g, 0.0423 mol) in chloroform (110.0 mL), bromine (2.18 mL, 0.0423 mol) was added slowly. After 3 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 purified with silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a colorless oil (**595**, 6.20 g, 70.2%).

Step 2 - (4-Bromo-2,5-difluoro-phenoxy)-tert-butyl-dimethyl-silane (596):

[0377] To 4-bromo-2,5-difluoro-phenol (**595**, 3.50 g, 0.0167 mol) in N,N-dimethylformamide (50.0 mL) were added tert-butyldimethylsilyl chloride (3.83 g, 0.0254 mol) and 1H-imidazole (6.00 g,

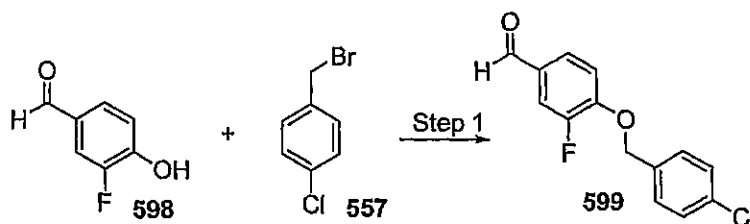
0.0529 mol). The reaction was stirred at room temperature overnight, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give the compound (**596**, 3.0 g, 55.4%).

Step 3 - 2,5-Difluoro-4-hydroxy-benzaldehyde (597):

[0378] To (4-bromo-2,5-difluoro-phenoxy)-tert-butyl-dimethyl-silane (**596**, 3.00 g, 9.28 mmol) in tetrahydrofuran (37.5 mL), under an atmosphere of nitrogen at -78 °C, n-butyllithium (3.90 mL, 2.50 M in hexane) was added slowly. After 30 minutes, N,N-dimethylformamide (0.825 mL, 0.0106 mol) was added to the reaction. One hour later, the reaction was allowed to come to room temperature. The reaction was poured into water and 1 N HCl, then 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 compound as an off-white solid (**597**, 0.86 g, 59.0%).

[0379] 4-(4-Chloro-benzyloxy)-3-fluoro-benzaldehyde **599** was synthesized in one step from 3-fluoro-4-hydroxy-benzaldehyde **598** as shown in Scheme 62.

Scheme 62

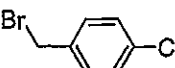
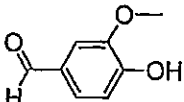
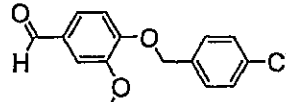
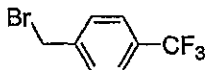
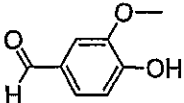
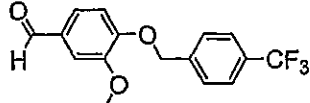
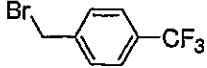
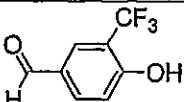
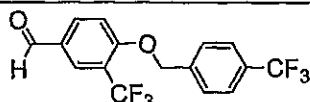
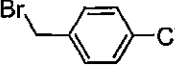
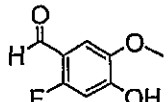
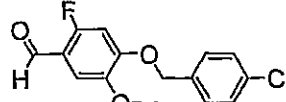
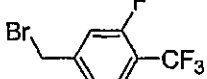
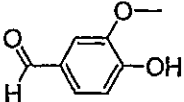
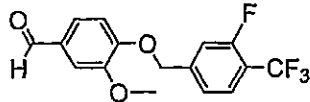
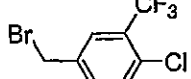
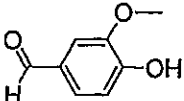
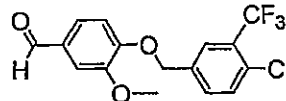
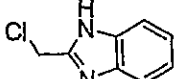
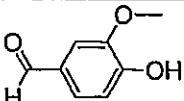
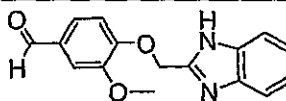
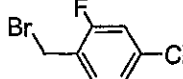
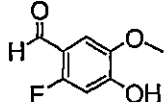
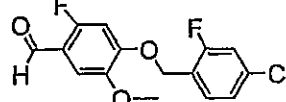
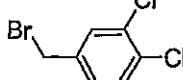
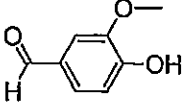
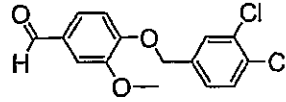
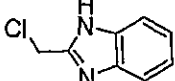
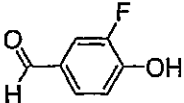
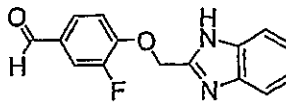
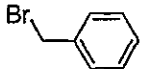
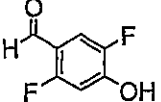
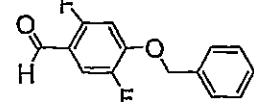
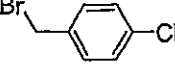
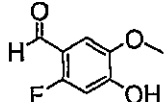
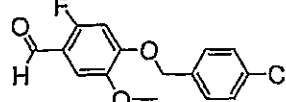


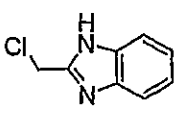
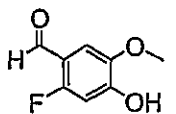
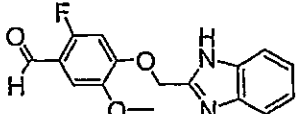
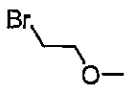
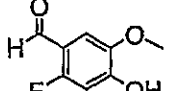
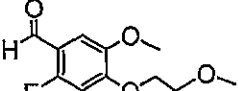
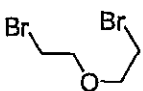
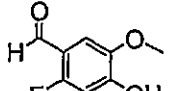
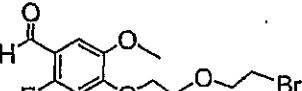
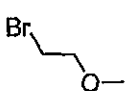
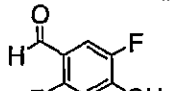
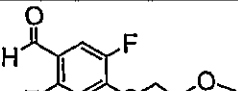
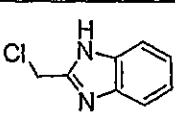
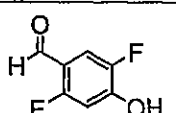
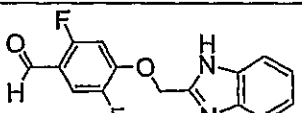
Step 1 – Synthesis of 4-(4-chloro-benzyloxy)-3-fluoro-benzaldehyde (599):

[0380] To 3-fluoro-4-hydroxy-benzaldehyde (**598**, 0.800 g, 5.71 mmol) in N,N-dimethylformamide (50.0 mL) was added sodium hydride (260.0 mg, 60% in mineral oil, 6.50 mmol). After 15 minutes, 4-chlorobenzyl bromide (**557**, 1.29 g, 6.28 mmol) was added to the reaction mixture. The reaction was stirred at 80 °C for 5 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 30% ethyl acetate in hexane to give the compound (**599**, 1.3 g, 86.0%).

[0381] Additional aldehydes were prepared using the protocol of Scheme 62, replacing either 4-chlorobenzyl bromide **557** with a suitable alkylating agent, and/or 3-fluoro-4-hydroxy-benzaldehyde **598** with a suitable aldehyde. The following table indicates the alkylating agent (column 1) and the

starting aldehyde (column 2) used to afford the aldehyde (column 3) synthesized following this protocol.

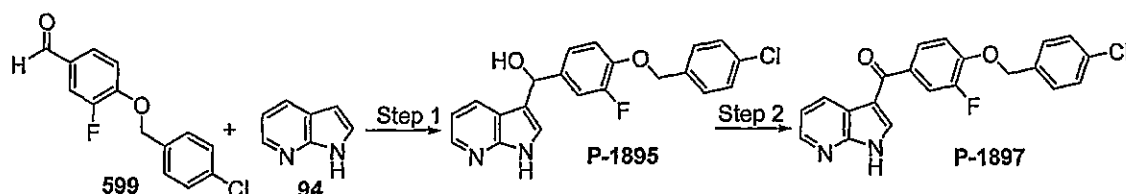
Alkylating agent	Aldehyde	Compound
		
		
		
		
		
		
		
		
		
		
		
		

Alkylating agent	Aldehyde	Compound
		
		
		
		
		

Example 35: Synthesis of [4-(4-chloro-benzyloxy)-3-fluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-1897 and related compounds

[0382] Compound P-1897 was synthesized in two steps from 4-(4-chloro-benzyloxy)-3-fluoro-benzaldehyde 599 as shown in Scheme 63.

Scheme 63



Step 1 – Synthesis of [4-(4-chloro-benzyloxy)-3-fluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (P-1895):

[0383] To 1H-Pyrrolo[2,3-b]pyridine (94, 100.0 mg, 0.85 mmol) in methanol (50.0 mL) were added 4-(4-chloro-benzyloxy)-3-fluoro-benzaldehyde (599, 250.0 mg, 0.94 mmol, prepared as described in Example 34) and potassium hydroxide (1.00g, 17.82 mmol) 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 30% ethyl acetate in hexane to give the compound (P-1895, 55 mg, 17.0%). MS(ESI) $[M+H]^+ = 383.3$.

Step 2 – Synthesis of [4-(4-chloro-benzyloxy)-3-fluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1897):

[0384] To [4-(4-chloro-benzyloxy)-3-fluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (P-1895, 17.7 mg, 0.046 mmol) in tetrahydrofuran (10.0 mL) was added Dess-Martin periodinane (23.5 mg, 0.056 mmol). The reaction was stirred at room temperature for 15 minutes. The reaction was concentrated, then purified with silica gel column chromatography eluting with 50% ethyl acetate in hexane to give a white solid (P-1897, 6.4 mg, 36.3%). MS(ESI) $[M+H]^+ = 381.3$.

[0385] Additional compounds were prepared using the protocol of Scheme 63, replacing 4-(4-chloro-benzyloxy)-3-fluoro-benzaldehyde 599 with a suitable aldehyde (prepared as described in Example 34), and optionally replacing 1H-Pyrrolo[2,3-b]pyridine 94 with an appropriate substituted 7-azaindole (see Example 9 or Example 16) in Step 1. The following compounds were made following this procedure:

[4-(4-Chloro-benzyloxy)-2-fluoro-5-methoxy-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1845),

[4-(4-Chloro-3-trifluoromethyl-benzyloxy)-3-methoxy-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1850),

[4-(4-Chloro-benzyloxy)-3-fluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1897),

[4-(1H-Benzoimidazol-2-ylmethoxy)-3-fluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1900),

(4-Benzyloxy-2,5-difluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1903),

[4-(1H-Benzoimidazol-2-ylmethoxy)-2-fluoro-5-methoxy-phenyl]-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1979),

[4-(1H-Benzoimidazol-2-ylmethoxy)-2-fluoro-5-methoxy-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1982),

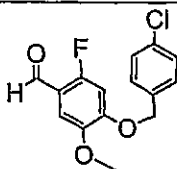
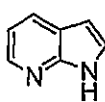
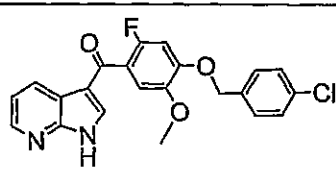
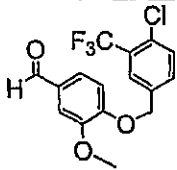
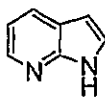
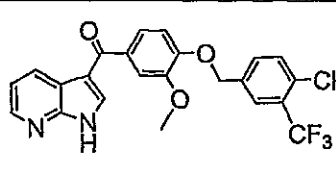
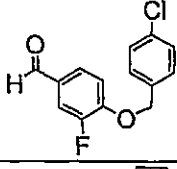
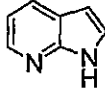
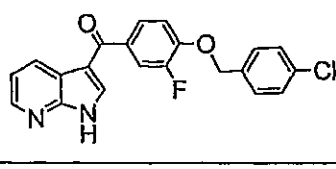
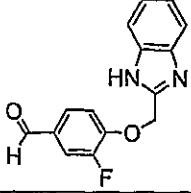
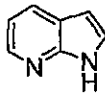
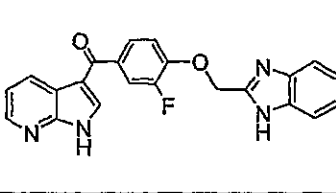
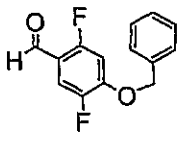
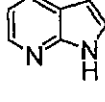
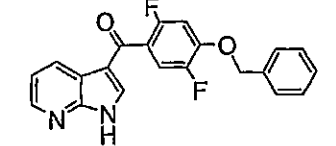
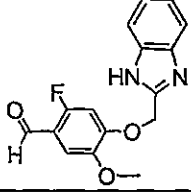
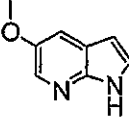
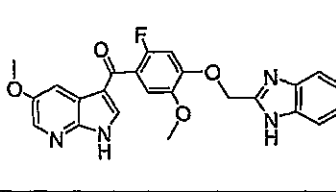
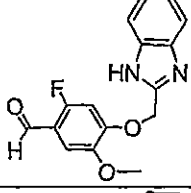
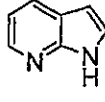
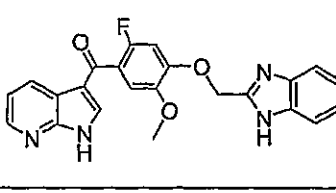
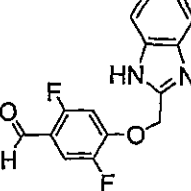
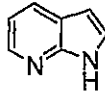
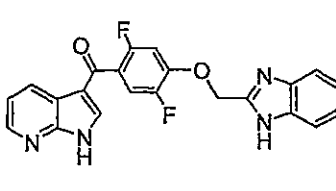
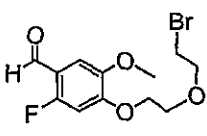
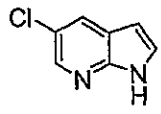
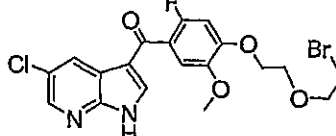
[4-(1H-Benzoimidazol-2-ylmethoxy)-2,5-difluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1987),

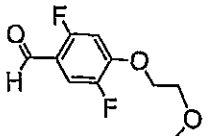
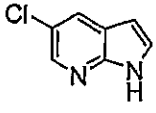
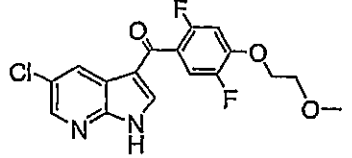
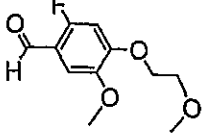
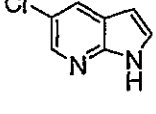
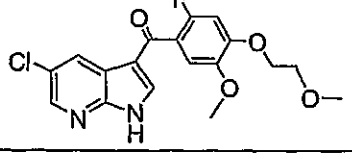
{4-[2-(2-Bromo-ethoxy)-ethoxy]-2-fluoro-5-methoxy-phenyl}-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1988),

(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2,5-difluoro-4-(2-methoxy-ethoxy)-phenyl]-methanone (P-1989), and

(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-[2-fluoro-5-methoxy-4-(2-methoxy-ethoxy)-phenyl]-methanone (P-1991).

The following table indicates the aldehyde (column 2) and the azaindole (column 3) used to afford the target compound (column 4). Column 1 indicates the compound number and column 5 the observed mass.

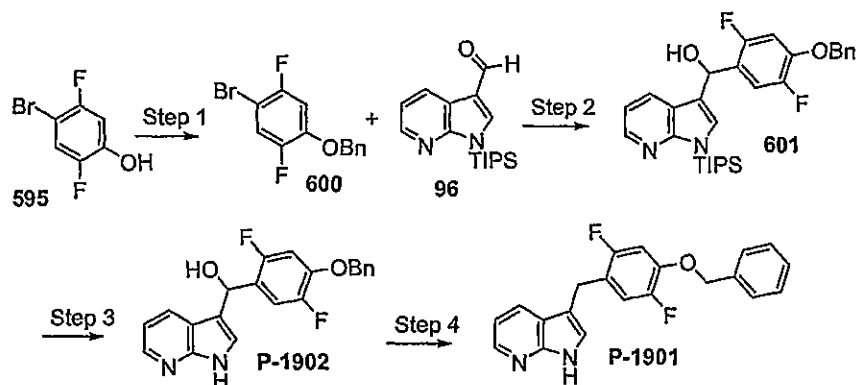
	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1845				409.6 [M-H] ⁺
P-1850				
P-1897				381.3
P-1900				387.4
P-1903				363.3 [M-H] ⁺
P-1979				447.4
P-1982				417.3
P-1987				405.3
P-1988				471.2 473.2

	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1989				365.2 [M-H] ⁺
P-1991				377.2 [M-H] ⁺

Example 36: Synthesis of 3-(4-Benzyloxy-2,5-difluoro-benzyl)-1H-pyrrolo[2,3-b]pyridine P-1901

[0386] Compound P-1901 was synthesized in four steps from 4-bromo-2,5-difluoro-phenol 595 as shown in Scheme 64.

Scheme 64



Step 1 – Synthesis of 1-Benzyloxy-4-bromo-2,5-difluoro-benzene (600):

[0387] To 4-bromo-2,5-difluoro-phenol (595, 0.90 g, 0.0043 mol, prepared as described in Example 34, Scheme 61) in N,N-dimethylformamide (30.0 mL) were added sodium hydride (0.21 g, 60% in mineral oil, 0.0052 mol) and benzyl bromide (0.563 mL, 0.00474 mol). 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 5% ethyl acetate in hexane to give a white solid (600, 0.84 g, 65.0%).

Step 2 - (4-Benzyloxy-2,5-difluoro-phenyl)-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (601):

[0388] To 1-Benzyloxy-4-bromo-2,5-difluoro-benzene (600, 0.84 g, 2.80 mmol) in tetrahydrofuran

(15.0 mL) and ether (15.0 mL), under an atmosphere of nitrogen at -78 °C, n-butyllithium (1.20 mL, 2.50 M in hexane) was added slowly. After 20 minutes, 1-Triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**96**, 0.82 g, 0.0027 mol, prepared as described in Example 18) was added to the reaction. After 20 minutes, the reaction was allowed to warm to room temperature 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 with silica gel column chromatography eluting with 20% ethyl acetate in hexane to a white solid (**601**, 1.0g, 70.0%). MS(ESI) $[M+H]^+ = 523.4$.

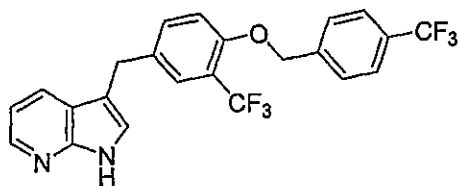
Step 3 – Synthesis of (4-Benzyloxy-2,5-difluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (P-1902):

[0389] To (4-Benzyloxy-2,5-difluoro-phenyl)-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**601**, 1.00 g, 1.91 mmol) in tetrahydrofuran (15.0 mL) was added tetrabutylammonium fluoride, trihydrate (0.63 g, 2.04 mmol). The reaction was stirred at room temperature for 10 minutes. The reaction was roto-evaporated and purified with silica gel column chromatography eluting with 50% ethyl acetate in hexane to give the compound as a white solid (**P-1902**, 0.59 g, 84.0%). MS(ESI) $[M+H]^+ = 367.4$.

Step 4 – Synthesis of 3-(4-Benzyloxy-2,5-difluoro-benzyl)-1H-pyrrolo[2,3-b]pyridine (P-1901):

[0390] To (4-Benzyloxy-2,5-difluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**P-1902**, 500.0 mg, 1.37 mmol) in acetonitrile (25.0 mL) were added triethylsilane (2.00 mL, 0.0125 mol) and trifluoroacetic acid (1.00 mL, 0.0130 mol). The reaction was heated to reflux for 2 hours. The reaction was concentrated and purified with silica gel column chromatography eluting with 50% ethyl acetate in hexane to give a white solid (**P-1901**, 60.0 mg, 94.1%). MS(ESI) $[M+H]^+ = 351.4$.

[0391] 3-[3-Trifluoromethyl-4-(4-trifluoromethyl-benzyloxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine **P-1797**

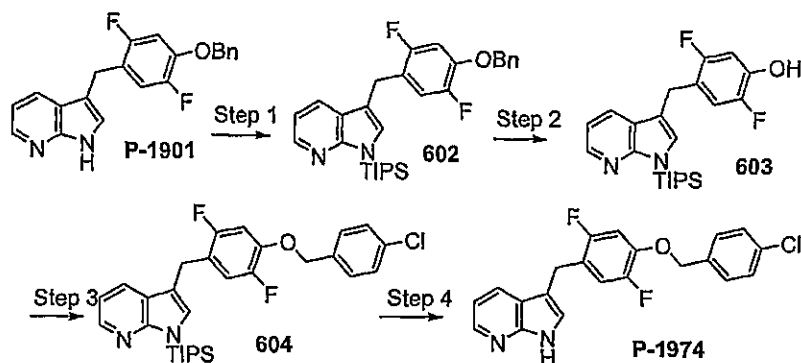


was prepared using the protocol of Scheme 64, substituting 4-bromo-2,5-difluoro-phenol **595** with 4-bromo-2-trifluoromethyl-phenol (prepared as described in Example 34, Scheme 61, Step 1, substituting 2,5-difluoro-phenol **594** with 2-trifluoromethyl-phenol) and benzyl bromide with 1-bromomethyl-4-trifluoromethyl-benzene in Step 1. MS(ESI) $[M+H]^+ = 451$.

Example 37: Synthesis of 3-[4-(4-chloro-benzyloxy)-2,5-difluoro-benzyl]-1H-pyrrolo[2,3-b]pyridine P-1974

[0392] Compound **P-1974** was synthesized in four steps from 3-(4-benzyloxy-2,5-difluoro-benzyl)-1H-pyrrolo[2,3-b]pyridine **P-1901** as shown in Scheme 65.

Scheme 65



Step 1 – Synthesis of 3-(4-Benzyloxy-2,5-difluoro-benzyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (602):

[0393] To 3-(4-Benzyloxy-2,5-difluoro-benzyl)-1H-pyrrolo[2,3-b]pyridine (**P-1901**, 560.0 mg, 1.60 mmol), prepared as described in Example 18, Scheme 33) in tetrahydrofuran (28.0 mL) was added sodium hydride (100.0 mg, 60% in mineral oil, 2.50 mmol). After 10 minutes, triisopropylsilyl chloride (0.500 mL, 2.36 mmol) was added to the reaction. After 4 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 30% ethyl acetate in hexane to give the compound (**602**, 0.70 g, 86.1%).

Step 2 – Synthesis of 2,5-difluoro-4-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenol (603):

[0394] To 3-(4-Benzyloxy-2,5-difluoro-benzyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (**602**, 0.70 g, 0.0014 mol) in methanol (30.0 mL) was added 50% palladium hydroxide on carbon (0.1 g) under an atmosphere of hydrogen. The reaction was stirred at room temperature overnight. The reaction was filtered and concentrated to give a colorless oil (**603**, 0.47 g, 82.0%).

Step 3 - 3-[4-(4-Chloro-benzyloxy)-2,5-difluoro-benzyl]-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (604):

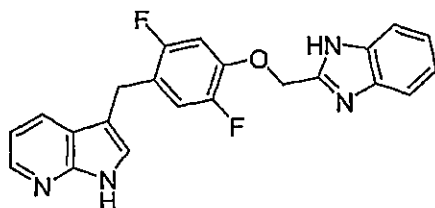
[0395] To 2,5-difluoro-4-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenol (**603**, 120.0 mg, 0.29 mmol) in N,N-dimethylformamide (15.0 mL) was added sodium hydride (18.0 mg, 60% in mineral oil, 0.45 mol) under an atmosphere of nitrogen. After 10 minutes, 4-chlorobenzyl

bromide (65.1 mg, 0.32 mol) was added to the reaction. The reaction was stirred at 40 °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 to give the crude compound (604, 0.15 g) that was used directly in the next step.

Step 4 – Synthesis of 3-[4-(4-chloro-benzyloxy)-2,5-difluoro-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1974):

[0396] To 3-[4-(4-chloro-benzyloxy)-2,5-difluoro-benzyl]-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (604, 0.150 g, 0.28 mmol) in tetrahydrofuran (10.0 mL) was added tetra-*n*-butylammonium fluoride (80.0 mg, 0.31 mmol). After 10 minutes, the reaction was concentrated and purified by silica gel column chromatography eluting with 50% ethyl acetate in hexane to give the compound as a white solid (P-1974, 30.8 mg, 28.9%). MS(ESI) $[M+H]^+ = 385.3$.

[0397] 2-[2,5-Difluoro-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenoxy-methyl]-1H-benzimidazole P-1975

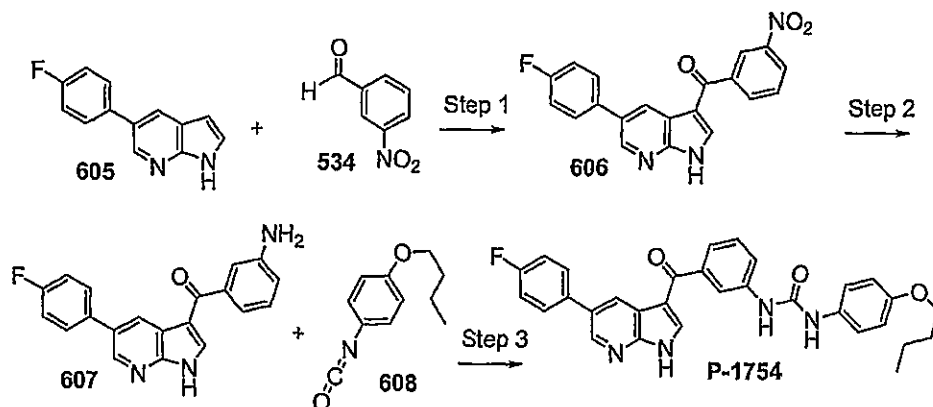


was prepared using the protocol of Scheme 65, substituting 4-chlorobenzyl bromide with 2-chloromethyl-1H-benzimidazole in step 3. MS(ESI) $[M+H]^+ = 391.3$.

Example 38: Synthesis of 1-(4-Butoxy-phenyl)-3-{3-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea P-1754

[0398] Compound P-1754 was synthesized in three steps from 5-(4-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine 605 as shown in Scheme 66.

Scheme 66



Step 1 – Preparation of (3-chloro-phenyl)-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methanone (606):

[0399] To 5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine (**605**, 530 mg, 2.5 mmol, prepared as described in Example 23) dissolved in 20 mL of dioxane was added 3-nitrobenzaldehyde (**534**, 758 mg, 5 mmol) and potassium hydroxide (4 mL of 2.5M aqueous). The vial was shaken on an orbital shaker for 16 hrs and the dioxane was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous layer was neutralized with the addition of 1M HCl. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give yellow-orange oil (1.5g). The crude material was dissolved in dichloromethane (150 mL) and chilled to 0° C. With vigorous stirring, pyridinium chlorochromate (3.0 g, 14 mmol) was added slowly, maintaining the solution temperature at 0° C. After complete addition the solution was allowed to stir at ambient temperature for 1 hour. The resulting dark brown/black solution was diluted with chloroform and passed through a plug of silica. Elution with methanol gave 1.5 g of crude **606** that was carried on to the next step without further purification.

Step 2 – Preparation of (3-Amino-phenyl)-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methanone (607):

[0400] Crude (3-chloro-phenyl)-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methanone (**606**, 1.5 g) was dissolved in a minimal amount of methanol (~5 mL) and Pd/C (5%, ~10 mg) was added. The reaction mixture was shaken on a Parr shaker under 70 psi H₂ overnight. The reaction mixture was filtered through Celite® and concentrated under reduced pressure to give 1.4 g of crude **607** that was carried on to the next step without further purification.

Step 3 – Preparation of 1-(4-Butoxy-phenyl)-3-{[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea (P-1754):

[0401] To a solution of – (3-Amino-phenyl)-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methanone (**607**, 7.5 mg) in anhydrous pyridine (200 µL) was added neat 1-butoxy-4-isocyanato-

benzene (608, 1.6 mg) and the reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in DMSO (200 μ L) and purified using reverse phase HPLC with an acetonitrile/water gradient. MS(ESI) $[M+H]^+= 523.5$.

[0402] Additional compounds were prepared following the protocol of Scheme 66, optionally substituting 5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine 605 with a suitable azaindole in Step 1 and/or optionally substituting 1-butoxy-4-isocyanato-benzene 608 with a suitable isocyanate in Step 3. Azaindoles were purchased or prepared as described in Examples 9 or 17. The following compounds were prepared by this procedure:

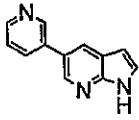
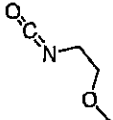
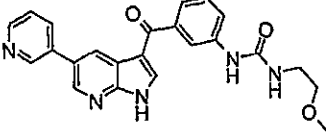
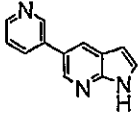
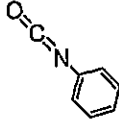
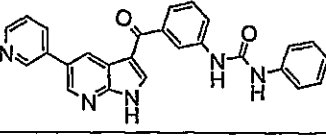
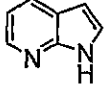
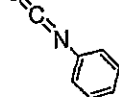
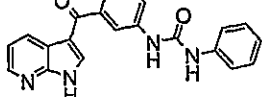
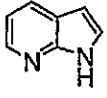
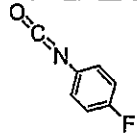
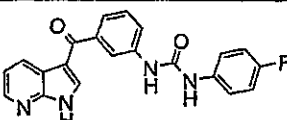
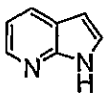
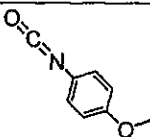
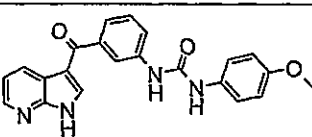
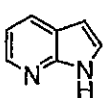
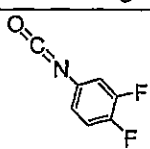
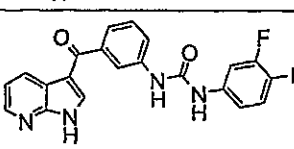
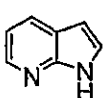
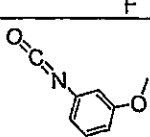
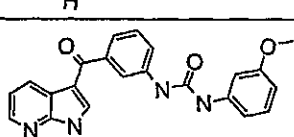
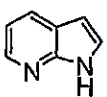
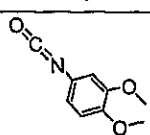
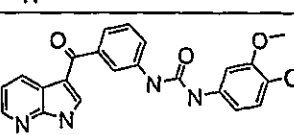
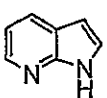
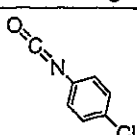
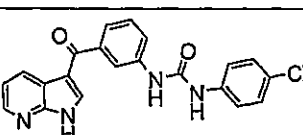
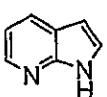
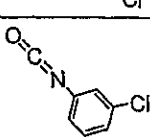
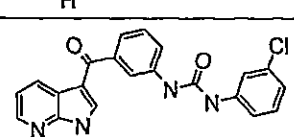
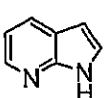
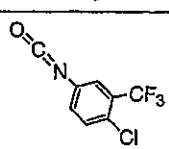
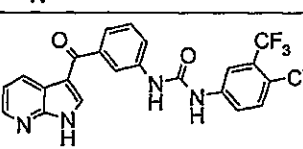
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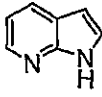
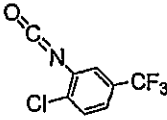
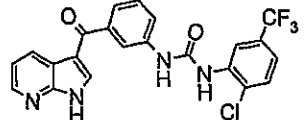
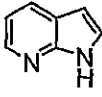
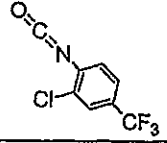
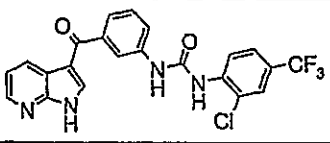
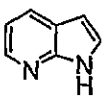
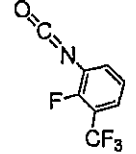
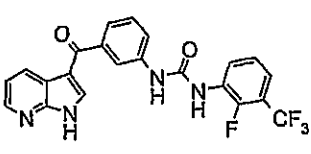
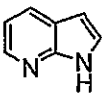
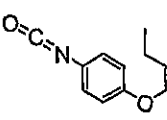
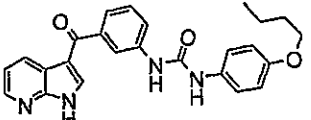
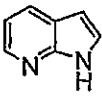
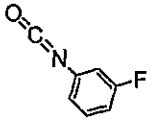
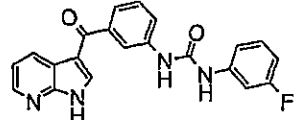
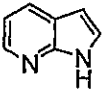
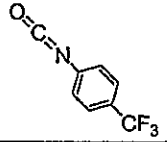
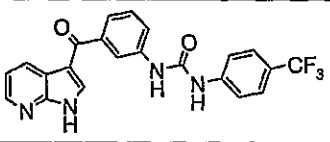
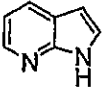
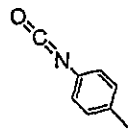
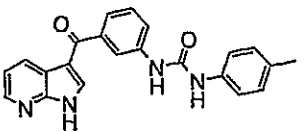
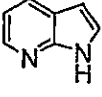
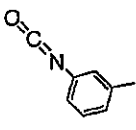
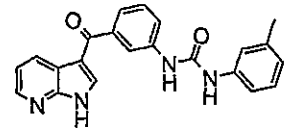
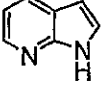
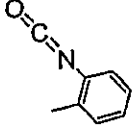
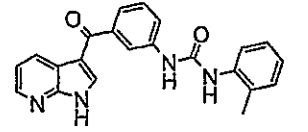
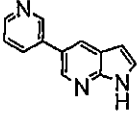
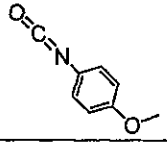
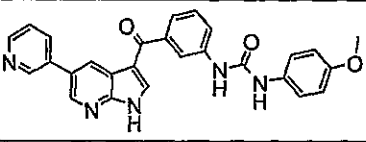
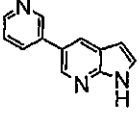
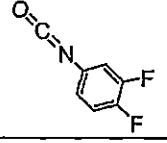
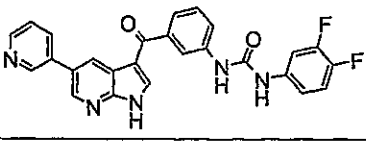
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- 1-(3,4-Dimethoxy-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1725),
- 1-(3-Chloro-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1726),
- 1-(2-Chloro-4-trifluoromethyl-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1727),
- 1-(2-Fluoro-3-trifluoromethyl-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1728),
- 1-(4-Butoxy-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1729),
- 1-(3-Fluoro-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1730),
- 1-[3-(5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea (P-1731),
- 1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1732),
- 1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-phenyl-urea (P-1733),
- 1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(4-methoxy-phenyl)-urea (P-1734),
- 1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(3,4-difluoro-phenyl)-urea (P-1735),
- 1-(3-Chloro-phenyl)-3-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1736),
- 1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea (P-1737),
- 1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(2-chloro-5-trifluoromethyl-phenyl)-urea (P-1738),
- 1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-urea (P-1739),
- 1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(2-fluoro-3-trifluoromethyl-phenyl)-urea (P-1740),
- 1-(4-Butoxy-phenyl)-3-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1741),
- 1-[3-(1H-Pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea (P-1746),

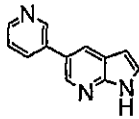
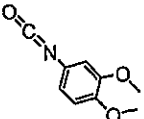
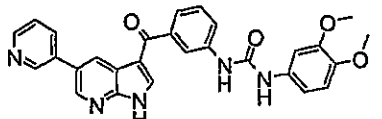
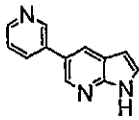
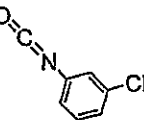
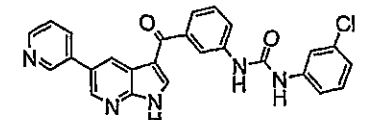
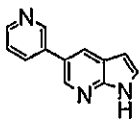
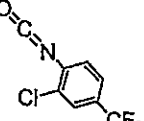
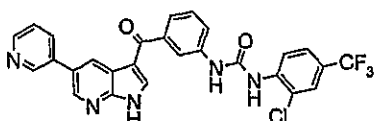
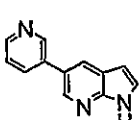
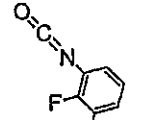
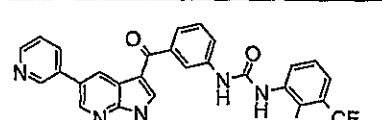
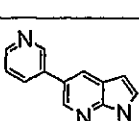
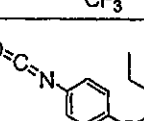
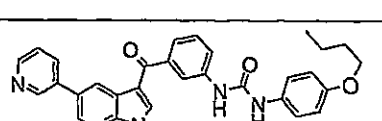
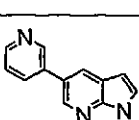
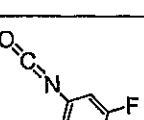
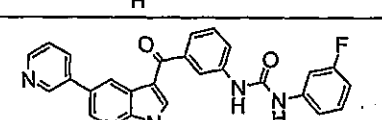
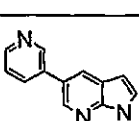
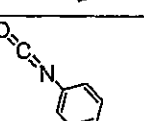
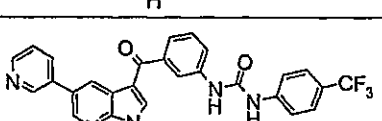
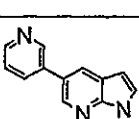
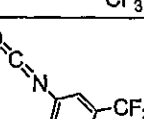
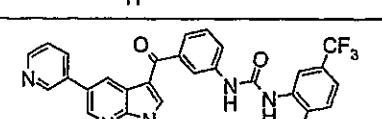
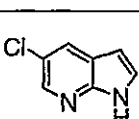
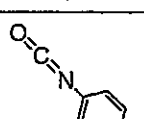
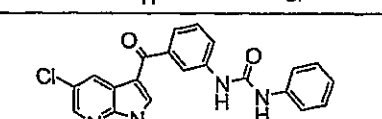
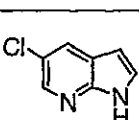
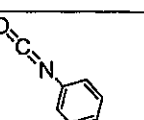
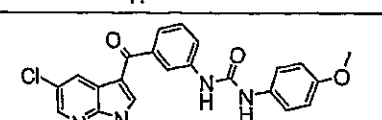
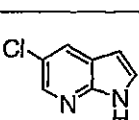
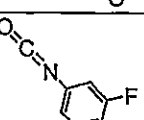
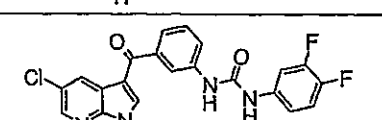
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- 1-(3-Methoxy-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1749),
- 1-(4-Chloro-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1750),
- 1-(4-Chloro-3-trifluoromethyl-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1751),
- 1-(2-Chloro-5-trifluoromethyl-phenyl)-3-{3-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea (P-1752),
- 1-(2-Chloro-4-trifluoromethyl-phenyl)-3-{3-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea (P-1753),
- 1-(4-Butoxy-phenyl)-3-{3-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea (P-1754),
- 1-[3-(5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea (P-1755),
- 1-[3-(5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-p-tolyl-urea (P-1756),
- 1-[3-(5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-m-tolyl-urea (P-1757),
- 1-{3-[5-(4-Fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-3-m-tolyl-urea (P-1758),
- 1-[3-(5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-o-tolyl-urea (P-1759),
- 1-Pyridin-4-yl-3-[3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1760),
- 1-(2-Methoxy-ethyl)-3-[3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1761),
- 1-(3-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1762),
- 1-(6-Methoxy-pyridin-3-yl)-3-[3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1763),
- 1-Isoxazol-3-yl-3-[3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1764),
- 1-(3-Methyl-isoxazol-5-yl)-3-[3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1765),
- 1-(3-Chloro-4-trifluoromethyl-phenyl)-3-[3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1766),
- 1-(3,4-Dimethyl-isoxazol-5-yl)-3-[3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1767),
- 1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-pyridin-4-yl-urea (P-1770),
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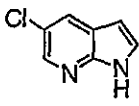
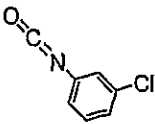
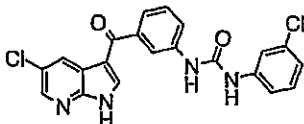
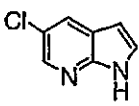
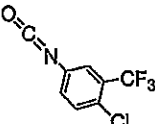
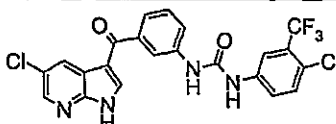
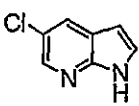
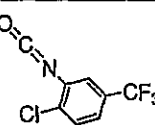
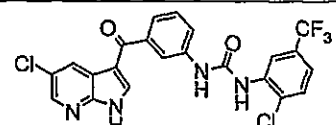
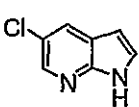
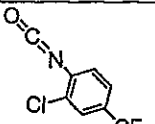
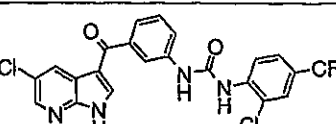
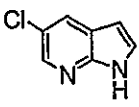
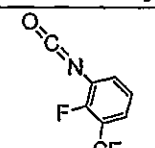
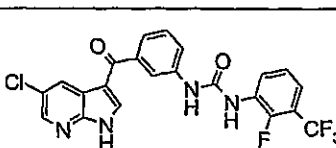
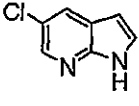
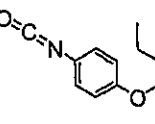
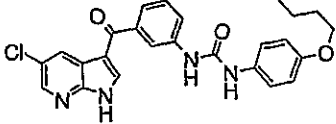
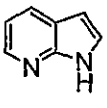
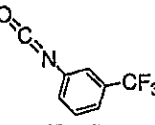
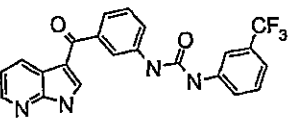
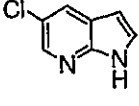
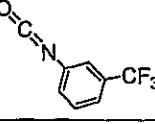
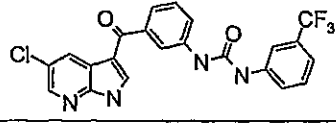
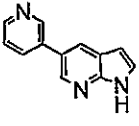
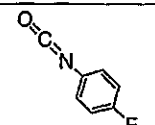
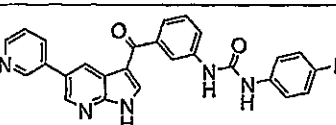
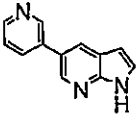
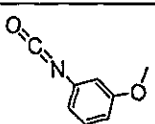
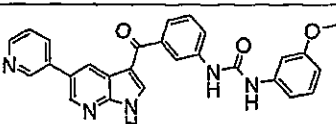
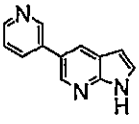
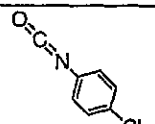
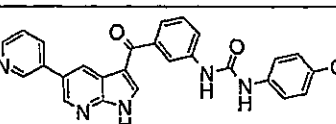
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1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(6-methoxy-pyridin-3-yl)-urea (P-1774),
1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-isoxazol-3-yl-urea (P-1775),
1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(3,4-dimethyl-isoxazol-5-yl)-urea (P-1776),
1-Pyridin-4-yl-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1777),
1-(3-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1778),
1-(6-Methoxy-pyridin-3-yl)-3-[3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1779),
1-(4-Dimethylamino-phenyl)-3-[3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1780),
1-Pyridin-3-yl-3-[3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-urea (P-1781),
1-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-(4-dimethylamino-phenyl)-urea (P-1782),
1-(4-Fluoro-phenyl)-3-{3-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea (P-1816),
1-(3,4-Difluoro-phenyl)-3-{3-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea (P-1817),
1-(3,4-Dimethoxy-phenyl)-3-{3-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea (P-1818), and
1-(3-Fluoro-phenyl)-3-{3-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-urea (P-1819).

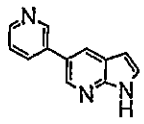
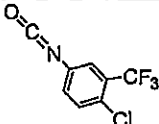
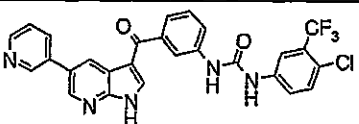
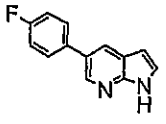
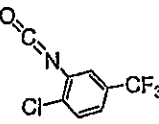
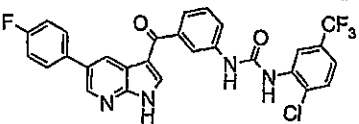
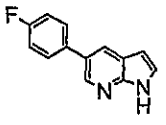
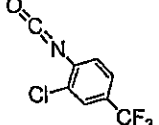
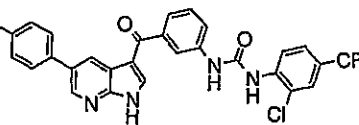
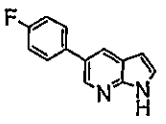
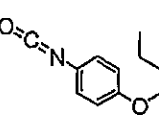
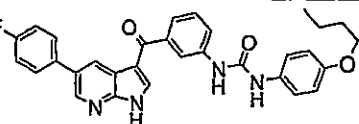
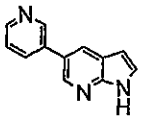
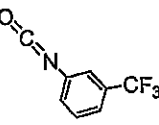
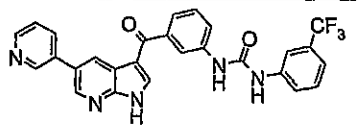
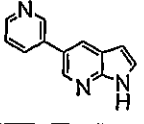
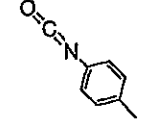
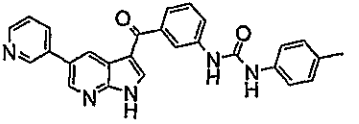
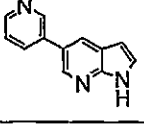
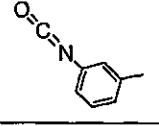
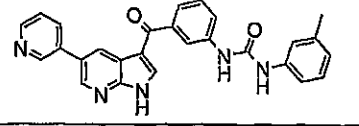
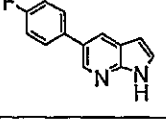
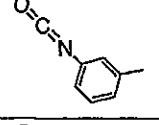
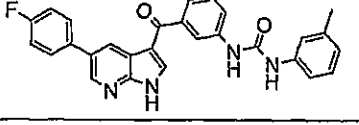
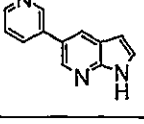
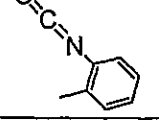
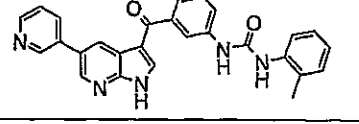
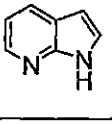
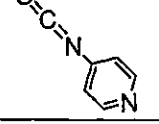
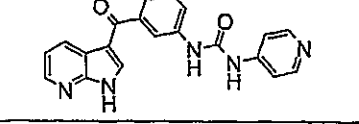
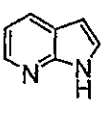
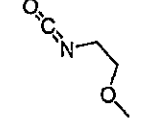
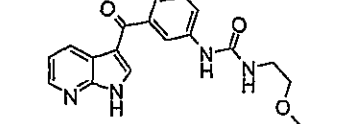
The following table indicates the azaindole (column 2) and isocyanate (column 3) used to afford the target compound (column 4). Column 1 provides the compound number and the observed mass is given in column 5.

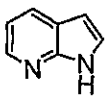
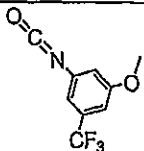
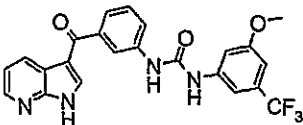
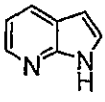
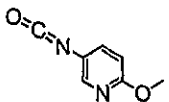
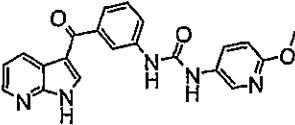
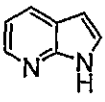
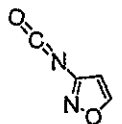
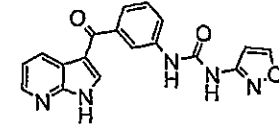
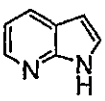
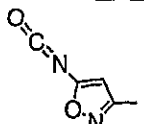
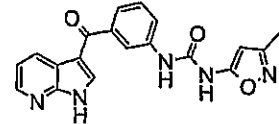
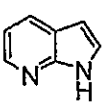
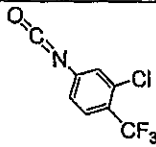
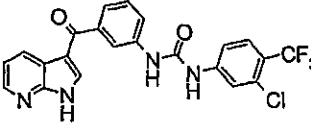
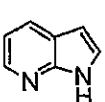
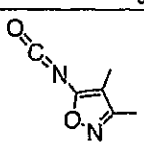
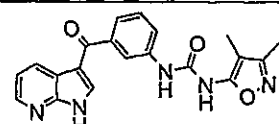
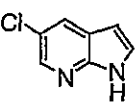
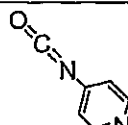
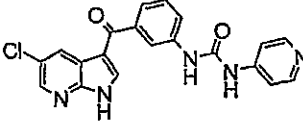
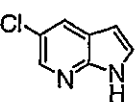
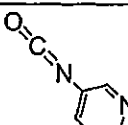
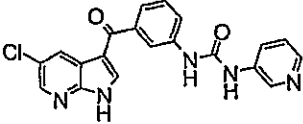
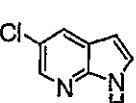
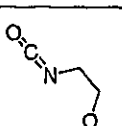
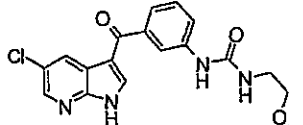
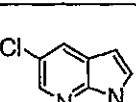
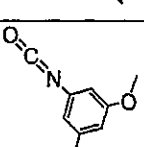
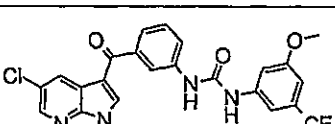
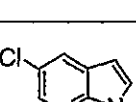
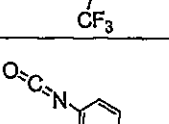
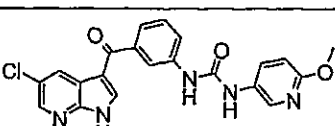
	Azaindole	Isocyanate	Compound	MS(ESI) [M+H] ⁺ observed
P-1566				416.3
P-1591				434.3
P-1703				357.1
P-1704				375.1
P-1705				387.1
P-1706				393.1
P-1707				387.1
P-1708				417.5
P-1709				391.1
P-1710				391.1
P-1711				459.1

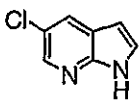
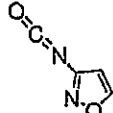
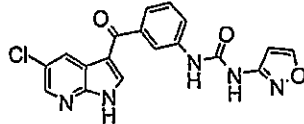
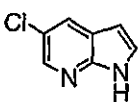
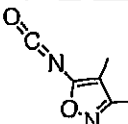
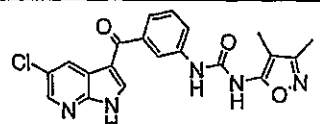
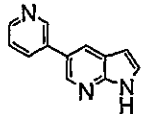
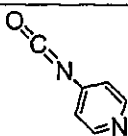
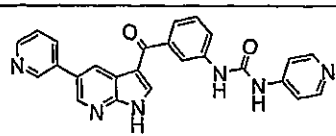
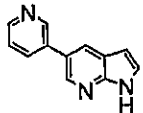
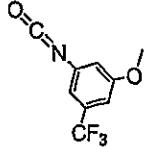
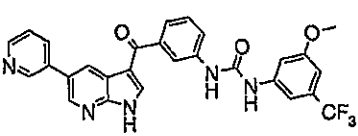
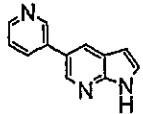
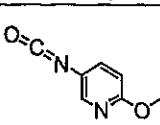
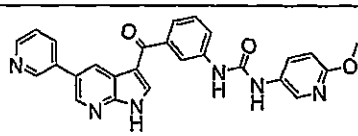
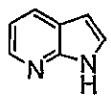
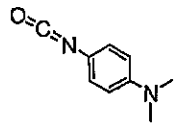
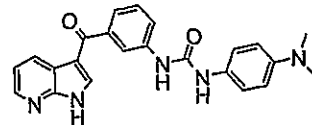
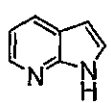
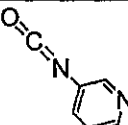
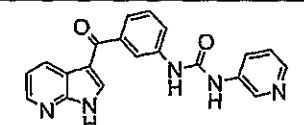
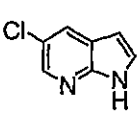
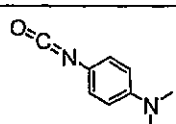
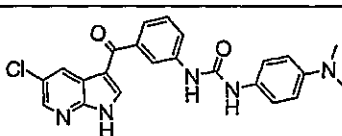
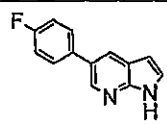
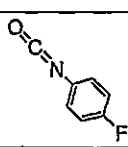
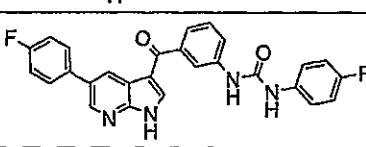
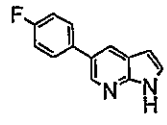
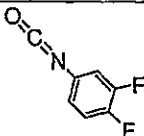
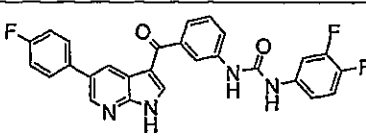
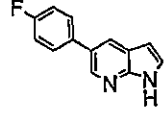
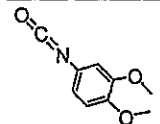
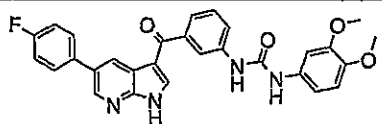
	Azaindole	Isocyanate	Compound	MS(ESI) [M+H] ⁺ observed
P-1712				459.1
P-1713				459.1
P-1714				443.1
P-1715				429.1
P-1716				375.1
P-1717				425.1
P-1718				371.1
P-1719				371.1
P-1720				371.1
P-1723				463.9
P-1724				470.3

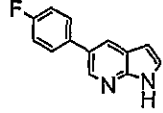
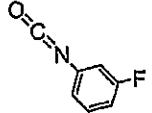
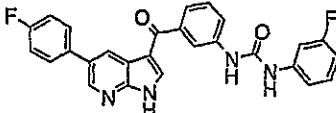
	Azaindole	Isocyanate	Compound	MS(ESI) [M+H] ⁺ observed
P-1725				494.3
P-1726				468.3
P-1727				535.9
P-1728				520.3
P-1729				505.9
P-1730				451.9
P-1731				502.3
P-1732				535.9
P-1733				391.1
P-1734				421.1
P-1735				427.1

	Azaindole	Isocyanate	Compound	MS(ESI) [M+H] ⁺ observed
P-1736				425.1
P-1737				493.1
P-1738				493.1
P-1739				493.1
P-1740				477.1
P-1741				463.1
P-1746				425.1
P-1747				459.1
P-1748				451.9
P-1749				463.9
P-1750				467.9

	Azaindole	Isocyanate	Compound	MS(ESI) [M+H] ⁺ observed
P-1751				535.9
P-1752				553.2
P-1753				553.2
P-1754				523.5
P-1755				502.3
P-1756				447.9
P-1757				447.9
P-1758				465.1
P-1759				447.9
P-1760				358.3
P-1761				339.1

	Azaindole	Isocyanate	Compound	MS(ESI) [M+H] ⁺ observed
P-1762				455.1
P-1763				388.3
P-1764				348.3
P-1765				362.3
P-1766				459.1
P-1767				376.3
P-1770				392.3
P-1771				392.3
P-1772				373.1
P-1773				489.1
P-1774				421.9

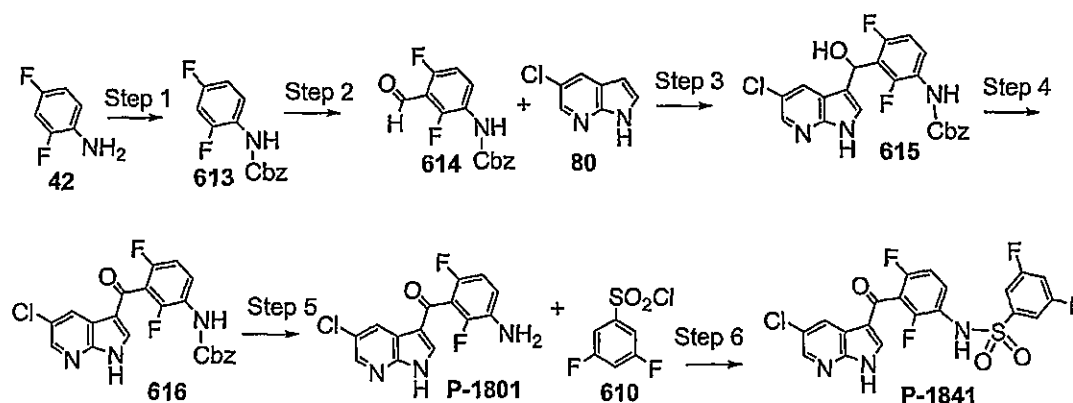
	Azaindole	Isocyanate	Compound	MS(ESI) [M+H] ⁺ observed
P-1775				382.3
P-1776				410.3
P-1777				435.1
P-1778				531.9
P-1779				465.1
P-1780				400.3
P-1781				358.3
P-1782				434.3
P-1816				468.1
P-1817				486.1
P-1818				510.2

	Azaindole	Isocyanate	Compound	MS(ESI) [M+H] ⁺ observed
P-1819				468.1

Example 39: Synthesis of N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-3,5-difluorobenzenesulfonamide P-1841

[0403] Compound P-1841 was synthesized in six steps from 2,4-difluoroaniline **42** as shown in Scheme 67.

Scheme 67



Step 1 - Preparation of (2,4-difluoro-phenyl)-carbamic acid benzyl ester (613):

[0404] To 2,4-difluoroaniline (**42**, 7.0 mL, 0.070 mol) in 100 mL of dichloromethane was added pyridine (11 mL, 0.14 mol) and benzyl chloroformate (11.9 mL, 0.0834 mol). The reaction mixture was stirred at ambient temperature for 1.5 hours. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and KHSO₄ solution. The organic layer was dried (MgSO₄), concentrated and crystallized from hexanes to give compound **613** (15.6 g, 85%).

Step 2 - Preparation of (2,4-difluoro-3-formyl-phenyl)-carbamic acid benzyl ester (614):

[0405] Into a round bottom flask was added (2,4-difluoro-phenyl)-carbamic acid benzyl ester (**613**, 3.83 g, 14.5 mmol) in tetrahydrofuran (148 mL, 1.82 mol). The solution was chilled to -78 °C and *n*-butyllithium (1.60 M in hexane, 19.1 mL, 30.0 mmol) was added over 30 minutes followed by the addition of, *N,N*-dimethylformamide (1.12 mL, 14.5 mol). The reaction mixture was allowed to warm to ambient temperature and was stirred overnight. 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 crystallized from ether to give compound **614** (3.0 g, 71%).

Step 3 - Preparation of {2,4-difluoro-3-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-carbamic acid benzyl ester (615):

[0406] Into a round bottom flask was added 5-chloro-1H-pyrrolo[2,3-b]pyridine (80, 0.524 g, 3.43 mmol, prepared as described in Example 9) in methanol (5.00 mL, 0.123 mol). Potassium hydroxide (0.800 g, 14.2 mmol) and (2,4-difluoro-3-formyl-phenyl)-carbamic acid benzyl ester (614, 1.02 g, 3.5 mmol) were added and the reaction mixture was stirred overnight. The reaction mixture was poured into 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and crystallized from ethyl acetate to give compound **615** (710 mg, 46%). MS(ESI)[M+H]⁺ = 444.

Step 4 - Preparation of [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-carbamic acid benzyl ester (616):

[0407] Into a round bottom flask was added {2,4-difluoro-3-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-carbamic acid benzyl ester (**615**, 1.01 g, 2.28 mmol) in tetrahydrofuran (5.00 mL, 0.0616 mol). Dess-Martin periodinane (1.20 g, 2.89 mmol) was added in portions. The reaction mixture was stirred at ambient temperature for 10 minutes, then 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 chromatography to give compound **616** (914 mg, 91%). MS(ESI)[M+H]⁺ = 442.

Step 5 - Preparation of (3-Amino-2,6-difluoro-phenyl)-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl) -methanone (P-1801):

[0408] [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-carbamic acid benzyl ester (**616**, 800 mg, 1.81 mmol) was added to 10 M NaOH (15.00 mL) and warmed to reflux overnight. The reaction mixture was diluted with 30 mL of water and was extracted with ethyl acetate to give compound **P-1801** (450 mg, 81%).

Step 6 - Preparation of N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3,5-difluorobenzenesulfonamide (P-1841)

[0409] Into a microwave reaction vessel were combined (3-Amino-2,6-difluoro-phenyl)-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl) -methanone (**P-1801**, 50 mg, 0.16 mmol, prepared as described in Example ???), 3,5-difluorobenzenesulfonyl chloride (**610**, 103 mg, 0.49 mmol), pyridine (0.5 mL, 6.1820 mol) and tetrahydrofuran (3.0 mL). The reaction was warmed in the CEM microwave at 300 watts, 130 °C for 10 minutes. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was collected, dried over Na₂SO₄, filtered and concentrated. The compound (**P-1841**) was isolated using column chromatography (silica, hexane:ethyl acetate 70:30) to obtain 36 mg (46%) compound. MS = 482.0.

[0410] Additional compounds were prepared following the protocol of Scheme 67 Step 6, optionally substituting (3-Amino-2,6-difluoro-phenyl)-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl) -methanone **P-1801** with (3-Amino-2,6-difluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl) -methanone **P-2021** (prepared per Scheme 67 Steps 1-5, substituting 5-chloro-1H-pyrrolo[2,3-b]pyridine **80** with 1H-pyrrolo[2,3-b]pyridine **94** in Step 3) and/or 3,5-difluorobenzenesulfonyl chloride **610** with an appropriate sulfonyl chloride. The following compounds were prepared by this procedure:

N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-isopropyl-benzenesulfonamide (**P-1839**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-0913**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-nitro-benzenesulfonamide (**P-1937**),

N-{4-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenylsulfamoyl]-phenyl}-acetamide (**P-1938**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-methoxy-benzenesulfonamide (**P-0958**),

5-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenylsulfamoyl]-furan-2-carboxylic acid methyl ester (**P-1941**),

5-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenylsulfamoyl]-2-methyl-furan-3-carboxylic acid methyl ester (**P-1942**),

5-Oxazol-5-yl-thiophene-2-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1943**),

5-Isoxazol-5-yl-thiophene-2-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1948**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,4-dimethoxy-benzenesulfonamide (**P-1951**),

2,5-Dimethyl-thiophene-3-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1952**),

2,5-Dimethyl-furan-3-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1953**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2-methyl-benzenesulfonamide (**P-1954**),

2,3-Dihydro-benzo[1,4]dioxine-6-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1955**),

2,4-Dimethyl-thiazole-5-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1956**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-0931**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-5-fluoro-2-methyl-benzenesulfonamide (**P-1961**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-methyl-benzenesulfonamide (**P-1962**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-oxazol-5-yl-benzenesulfonamide (**P-1963**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,5-dimethoxy-benzenesulfonamide (**P-1131**),

2-Cyano-N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-1965**),

3-Cyano-N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide (**P-1966**),

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-isopropyl-benzenesulfonamide (**P-1968**),

Benzothiazole-6-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-1969**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-methoxy-benzenesulfonamide (**P-2011**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide (**P-0885**),

Thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1267**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-methyl-benzenesulfonamide (**P-1842**),

N-{4-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenylsulfamoyl]-phenyl}-acetamide (**P-1905**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-methoxy-benzenesulfonamide (**P-0983**),

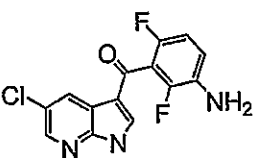
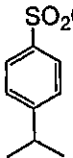
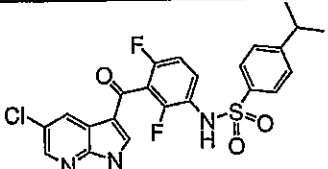
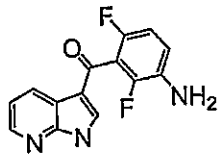
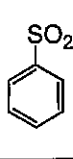
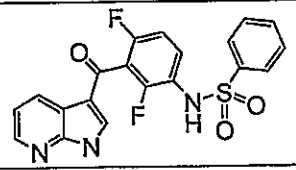
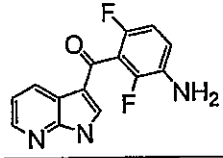
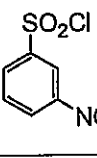
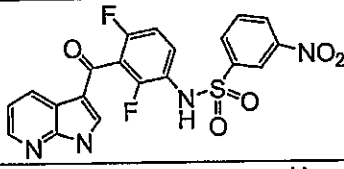
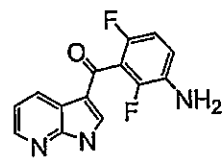
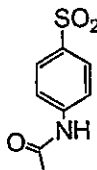
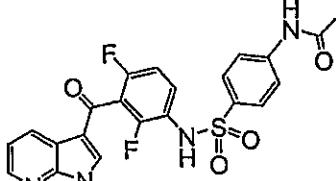
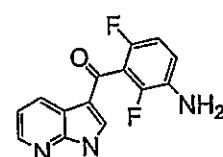
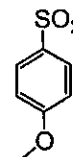
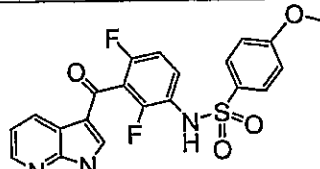
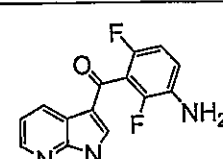
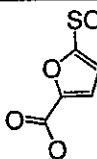
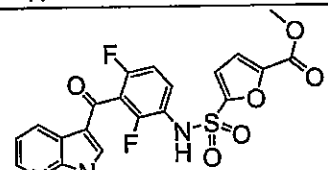
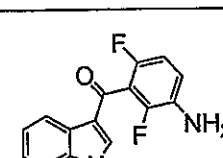
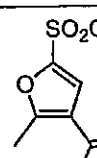
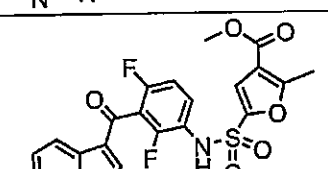
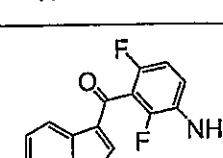
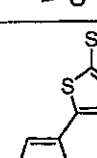
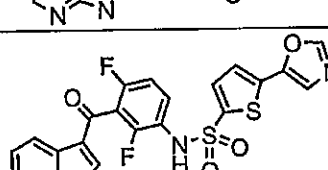
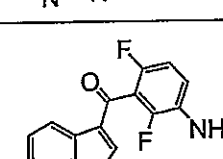
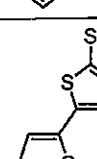
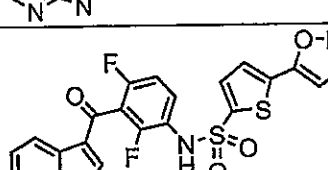
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-trifluoromethyl-benzenesulfonamide (**P-1599**),

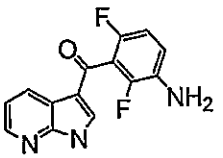
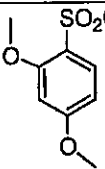
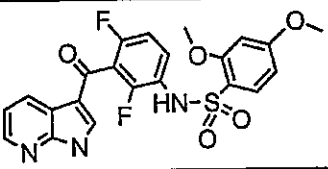
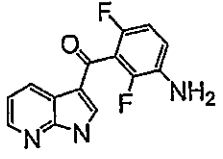
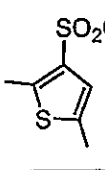
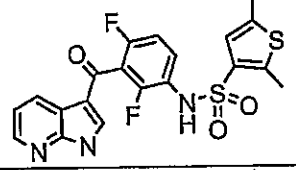
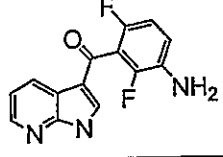
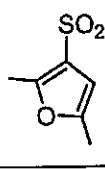
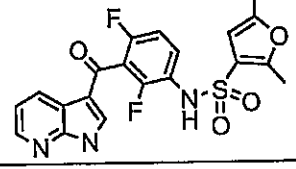
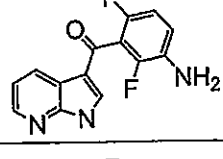
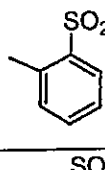
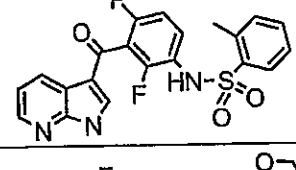
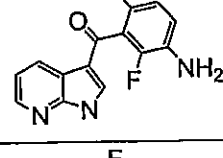
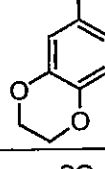
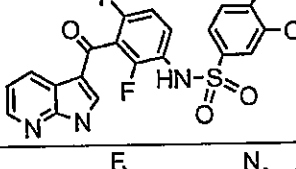
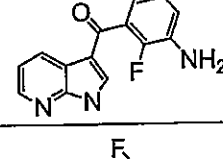
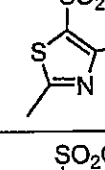
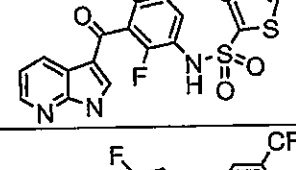
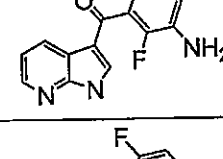
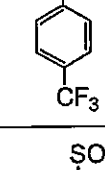
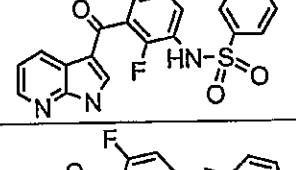
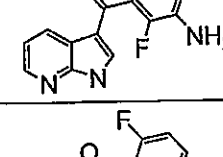
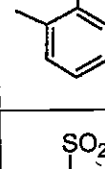
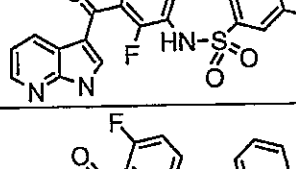
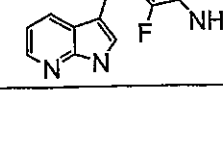
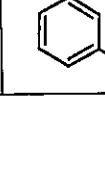
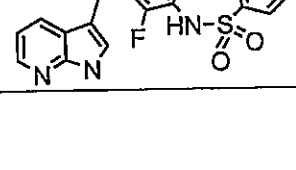
5-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenylsulfamoyl]-furan-2-carboxylic acid methyl ester (**P-1907**),

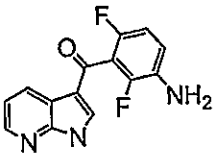
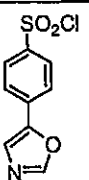
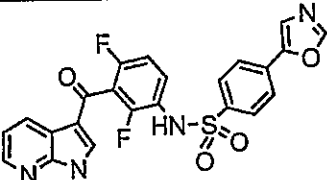
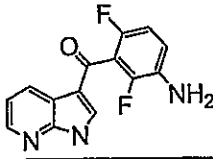
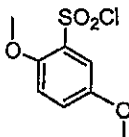
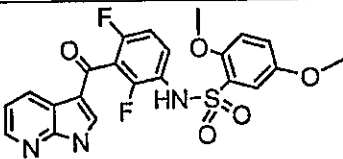
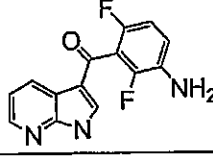
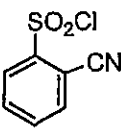
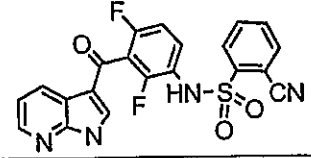
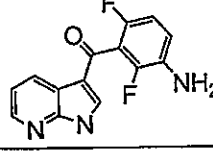
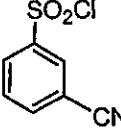
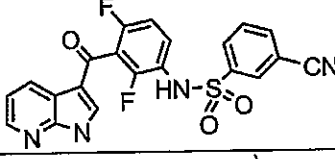
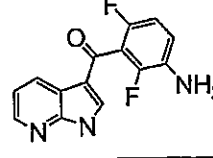
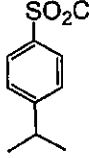
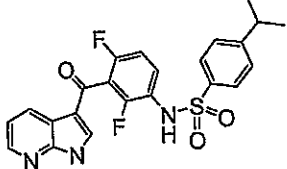
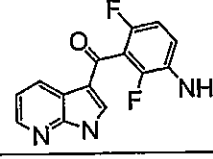
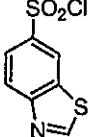
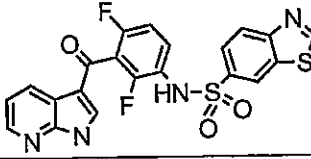
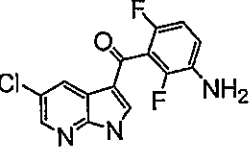
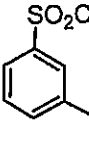
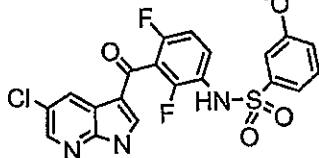
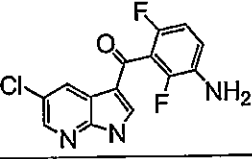
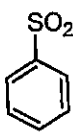
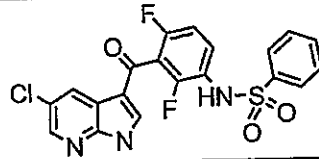
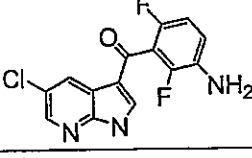
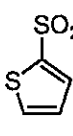
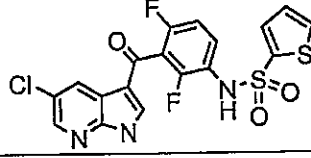
5-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenylsulfamoyl]-2-methyl-furan-3-carboxylic acid methyl ester (**P-1908**),

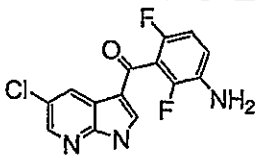
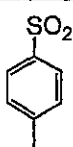
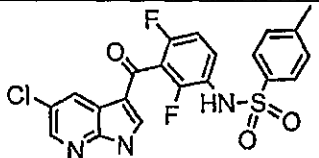
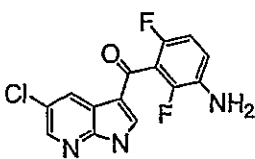
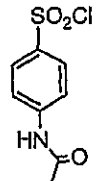
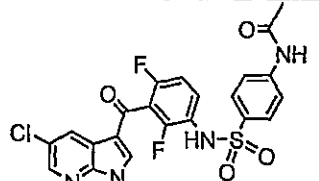
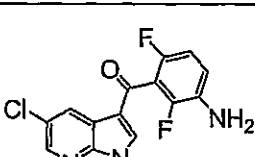
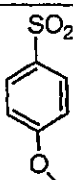
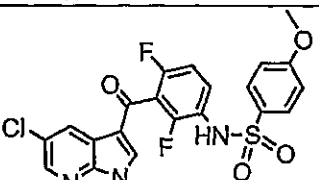
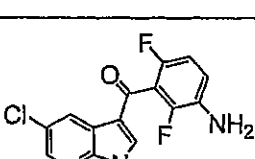
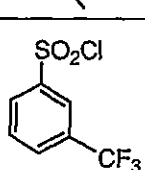
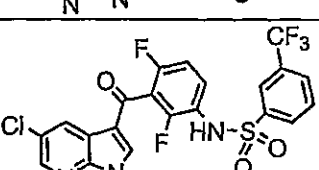
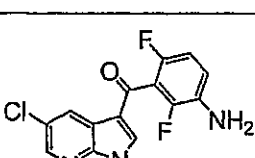
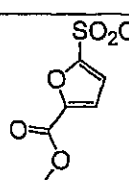
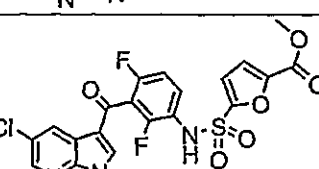
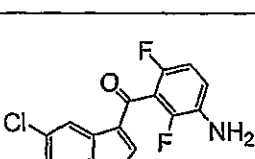
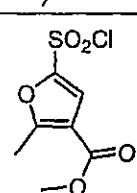
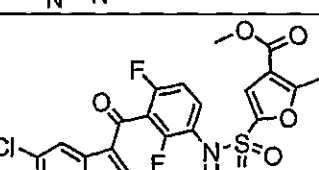
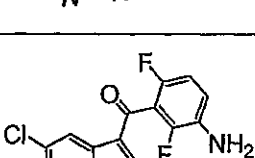
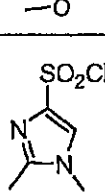
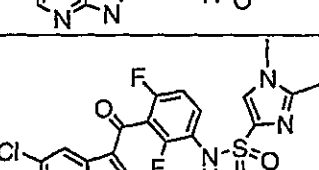
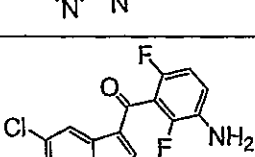
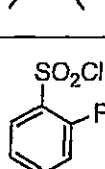
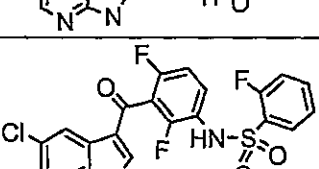
1,2-Dimethyl-1H-imidazole-4-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1911**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide (**P-1912**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-difluoromethoxy-benzenesulfonamide (**P-1916**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,4-dimethoxy-benzenesulfonamide (**P-1918**),
2,5-Dimethyl-thiophene-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1919**),
2,5-Dimethyl-furan-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1920**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2-methyl-benzenesulfonamide (**P-1921**),
2,3-Dihydro-benzo[1,4]dioxine-6-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1922**),
2,4-Dimethyl-thiazole-5-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-1923**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,4-difluoro-benzenesulfonamide (**P-1926**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-5-fluoro-2-methyl-benzenesulfonamide (**P-1927**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-methyl-benzenesulfonamide (**P-1928**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-dimethoxy-benzenesulfonamide (**P-1929**),
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2-cyano-benzenesulfonamide (**P-1931**), and
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-cyano-benzenesulfonamide (**P-1932**).

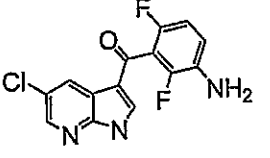
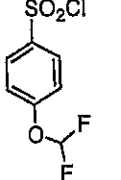
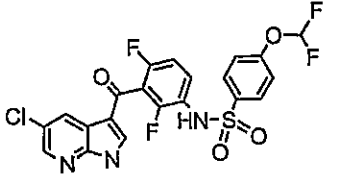
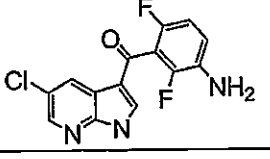
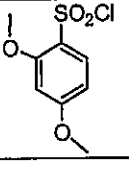
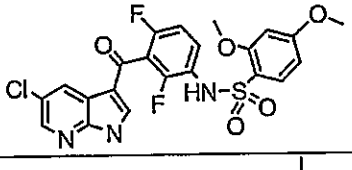
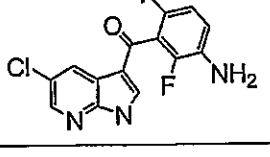
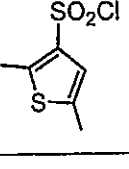
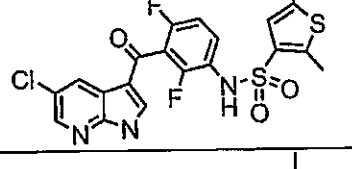
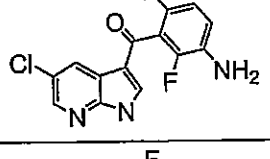
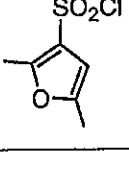
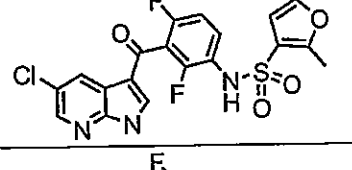
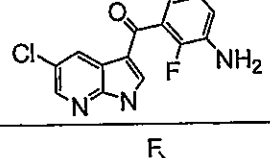
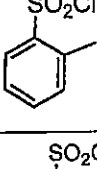
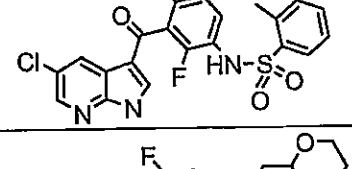
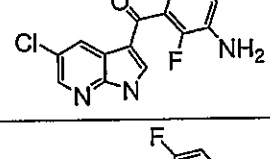
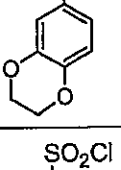
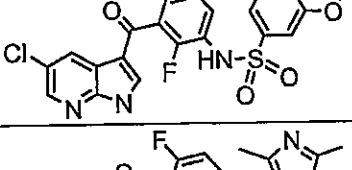
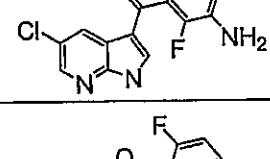
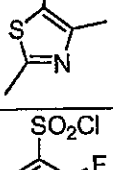
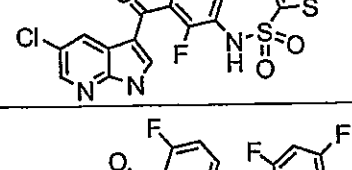
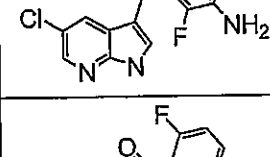
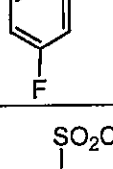
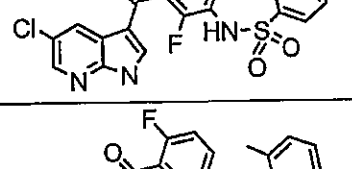
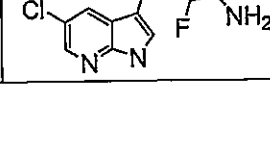
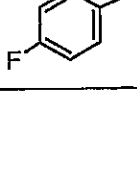
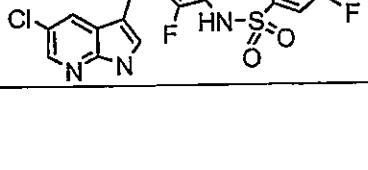
The following table indicates the azaindole (column 2) and the sulfonyl chloride (column 3) used to afford the target compound (column 4). The compound number is provided in column 1, with the observed mass given in column 5.

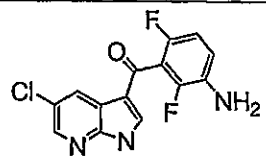
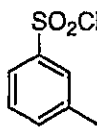
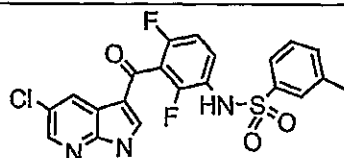
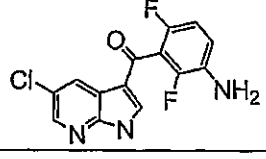
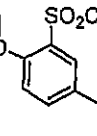
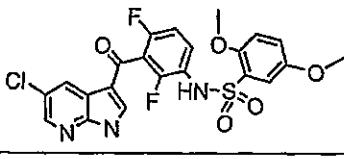
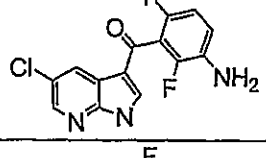
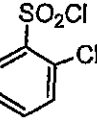
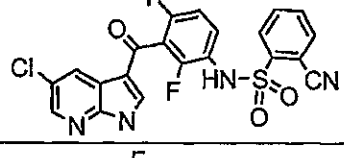
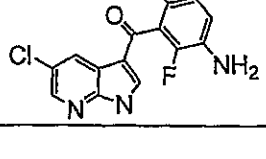
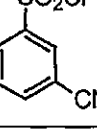
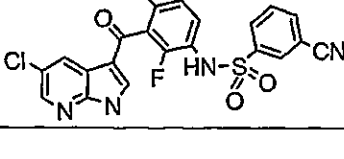
	Azaindole	Sulfonyl chloride	Compound	MS(ESI) [M+H] ⁺ observed
P-1839				489.9
P-0913				413.9
P-1937				459.1
P-1938				471.1
P-0958				444.3
P-1941				462.3
P-1942				475.9
P-1943				487.1
P-1948				487.1

	Azaindole	Sulfonyl chloride	Compound	MS(ESI) [M+H] ⁺ observed
P-1951				473.9
P-1952				447.9
P-1953				432.3
P-1954				427.9
P-1955				472.3
P-1956				448.7
P-0931				481.9
P-1961				445.9
P-1962				427.9

	Azaindole	Sulfonyl chloride	Compound	MS(ESI) [M+H] ⁺ observed
P-1963				481.1
P-1131				473.9
P-1965				439.1
P-1966				439.1
P-1968				456.3
P-1969				471.1
P-2011				477.9
P-0885				447.9
P-1267				453.9

	Azaindole	Sulfonyl chloride	Compound	MS(ESI) [M+H] ⁺ observed
P-1842				462.3
P-1905				505.1
P-0983				477.9
P-1599				515.9
P-1907				496.3
P-1908				509.9
P-1911				466.3
P-1912				465.9

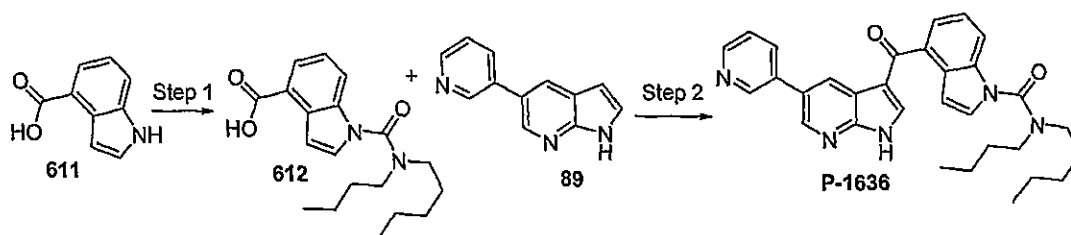
	Azaindole	Sulfonyl chloride	Compound	MS(ESI) [M+H] ⁺ observed
P-1916				513.9
P-1918				
P-1919				481.9
P-1920				465.9
P-1921				461.9
P-1922				505.9
P-1923				483.1
P-1926				483.9
P-1927				479.9

	Azaindole	Sulfonyl chloride	Compound	MS(ESI) [M+H] ⁺ observed
P-1928				461.9
P-1929				507.9
P-1931				473.1
P-1932				473.1

Example 40: Synthesis of 4-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid dibutylamide P-1636

[0411] Compound P-1636 was synthesized in two steps from 1H-indole-4-carboxylic acid 611 as shown in Scheme 68.

Scheme 68



Step 1 – Preparation of 1-dibutylcarbamoyl-1H-indole-4-carboxylic acid (612):

[0412] To 1H-Indole-4-carboxylic acid (611, 251 mg, 1.56 mmol) in tetrahydrofuran (3 mL), was added 2.5M n-butyllithium in hexane (1.28 mL, 3.19 mmol) at -78 °C. After 30 minutes, dibutyl carbamyl chloride (657 mg, 3.43 mmol) was added and stirred for two hours. The reaction solution was quenched with 1M HCl (aq.) and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtrated and concentrated. The desired

compound was isolated with silica gel column chromatography using 10% ethyl acetate in hexane to give a white solid (**612**, 88 mg, 18%). MS(ESI) $[M-H]^+ = 315.1$.

Step 2 – Preparation of 4-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid dibutylamide (P-1636):

[0413] To 1-dibutylcarbamoyl-1H-indole-4-carboxylic acid (**612**, 78 mg, 0.25 mmol) in dichloromethane (2 mL), thionyl chloride (25 μ L, 0.34 mmol) was added and stirred for one hour, followed by rotary evaporation to remove solvents to provide the dried acid chloride, which was dissolved in dichloromethane for later use. Meanwhile, 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**89**, 55 mg, 0.28 mmol, prepared as described in Example 17) in dichloromethane (8 mL), was mixed with aluminum trichloride (215 mg, 1.6 mmol) and stirred for one hour, followed by addition of the dried acid chloride in dichloromethane (3 mL). The reaction was stirred at room temperature overnight, then quenched with methanol and all volatiles were removed. The desired compound was isolated with silica gel column chromatography using 10% methanol in dichloromethane to give a solid (**P-1636**, 11 mg, 9%). MS(ESI) $[M+H]^+ = 494.3$.

[0414] Additional compounds were prepared following the protocol of Scheme 68, substituting dibutyl carbamyl chloride with a suitable reagent in Step 1 and optionally substituting 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **89** with 5-(6-Methoxy-pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine (see Example 17) in Step 2. The following compounds were prepared following this procedure:

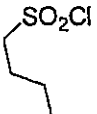
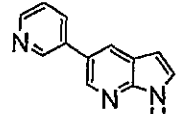
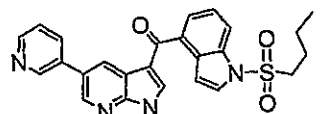
1-(Butane-1-sulfonyl)-1H-indol-4-yl)-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-1661**),

4-(5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid pentylamide (**P-1702**),

4-(5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-indole-1-carboxylic acid dipropylamide (**P-1722**), and

4-[5-(6-Methoxy-pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-indole-1-carboxylic acid butylamide (**P-1827**).

The following table indicates the reagent used in place of dibutyl carbamyl chloride (column 2) and the azaindole (column 3) used to afford the target compound (column 3). The compound number is provided in column 1, and the observed mass is given in column 5.

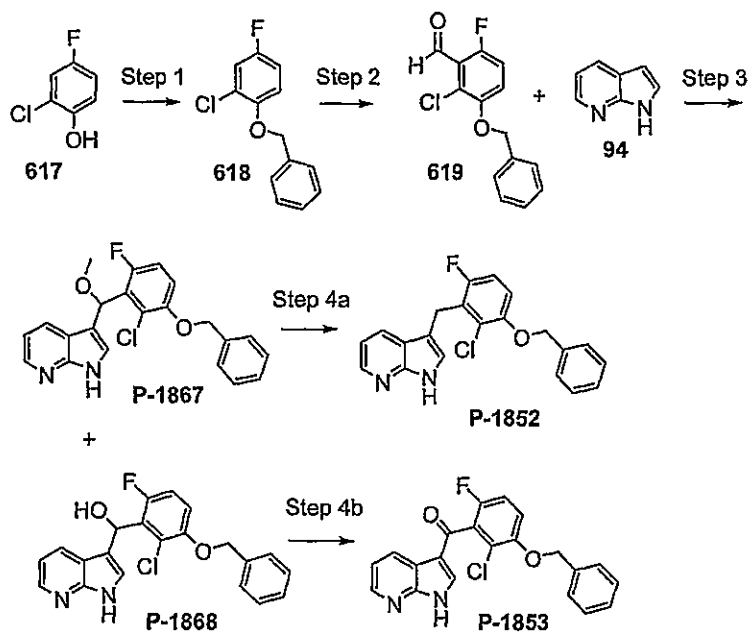
	Step 1 reagent	Azaindole	Compound	MS(ESI) $[M+H]^+$ observed
P-1661				459.2

	Step 1 reagent	Azaindole	Compound	MS(ESI) [M+H] ⁺ observed
P-1702				452.3
P-1722				466.3
P-1827				468.3

Example 41: Synthesis of 3-(3-Benzyloxy-2-chloro-6-fluoro-benzyl)-1H-pyrrolo[2,3-*b*]pyridine P-1852, (3-Benzyloxy-2-chloro-6-fluoro-phenyl)-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)-methanone P-1853 and related compounds

[0415] Compounds **P-1852** and **P-1853** were synthesized in four steps from 2-chloro-4-fluorophenol **617** and 1H-pyrrolo[2,3-*b*]pyridine **94** as shown in Scheme 67.

Scheme 69



Step 1 – Preparation of 1-Benzyloxy-2-chloro-4-fluoro-benzene (618):

[0416] To a solution of 2-chloro-4-fluorophenol (**617**, 7 g, 0.05 mol) in tetrahydrofuran (100 mL) was added sodium hydride (1.8 g, 95% dry powder, 0.071 mol) at room temperature over 15 minutes under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 30 minutes. Benzyl bromide (10 g, 0.060 mol) was added slowly to the reaction mixture, then stirred at room temperature overnight. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with hydrochloric acid (10%), water, 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 compound as a white solid (**618**, 7.6 g, 60%).

Step 2 – Preparation of 3-Benzyloxy-2-chloro-6-fluoro-benzaldehyde (619):

[0417] To a solution of 1-benzyloxy-2-chloro-4-fluoro-benzene (**618**, 5.8 g, 0.024 mol) in tetrahydrofuran (100 mL) was added 2.50 M of n-butyllithium (2.7 mL, 2.50 M in hexane, 0.029 mol) slowly at -78 °C over 15 minutes under nitrogen. The reaction mixture was stirred at -78 °C for 30 minutes. To the reaction mixture was then added N,N-dimethylformamide (4.2 mL, 0.054 mol). The reaction was allowed to warm to room temperature and was continued at room temperature overnight. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with hydrochloric acid (10%), water, 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 a white solid (**619**, 2.1 g, 32%). MS(ESI) $[M+H]^+ = 265.08$.

Step 3 – Preparation of 3-[(3-Benzyloxy-2-chloro-6-fluoro-phenyl)-methoxy-methyl]-1H-pyrrolo[2,3-b]pyridine (P-1867) and (3-Benzyloxy-2-chloro-6-fluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl) – methanol (P-1868):

[0418] A mixture of 1H-pyrrolo[2,3-b]pyridine (**94**, 0.5 g, 4 mmol), 3-benzyloxy-2-chloro-6-fluoro-benzaldehyde (**619**, 1.3 g, 4.9 mmol), and potassium hydroxide (0.99 g, 18 mmol) in methanol (30 mL) was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate and water. The organic layer was collected and washed with brine. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide compound **P-1867** as a white solid (1.3 g, 70%, MS(ESI) $[M+H]^+ = 397.16$), and compound **P-1868** as an off-white solid (0.2 g, 10, MS(ESI) $[M+H]^+ = 383.14$).

Step 4a – Preparation of 3-(3-Benzyloxy-2-chloro-6-fluoro-benzyl)-1H-pyrrolo[2,3-b]pyridine (P-1852):

[0419] A mixture of 3-[(3-Benzyloxy-2-chloro-6-fluoro-phenyl)-methoxy-methyl]-1H-pyrrolo[2,3-b]pyridine (**P-1867**, 0.1 g, 0.2 mmol), trifluoroacetic acid (0.6 mL, 8 mmol), and triethylsilane (0.3 mL, 2 mmol) in acetonitrile (10 mL) was refluxed for 2 hours. The mixture was concentrated and the

residue was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate, 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 compound as an off-white solid (**P-1852**, 62 mg, 70%). MS(ESI) $[M+H]^+ = 367.16$.

Step 4b – Preparation of (3-Benzoyloxy-2-chloro-6-fluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl) - methanone (P-1853):

[0420] To a solution of (3-Benzoyloxy-2-chloro-6-fluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**P-1868**, 65 mg, 0.17 mmol) in tetrahydrofuran (10 mL) was added Dess-Martin periodinane (79 mg, 0.19 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched with a saturated solution of sodium thiosulfate, extracted with ethyl acetate, washed with sodium bicarbonate, brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide the compound as a light yellow solid (**P-1853**, 32 mg, 50%). MS(ESI) $[M+H]^+ = 381.13$.

[0421] Additional compounds were prepared following the protocol of Scheme 69, optionally replacing 2-chloro-4-fluorophenol **617** with 2, 6-difluorophenol or 2, 6-dichlorophenol, optionally replacing benzyl bromide with an appropriate substituted benzyl bromide, and optionally replacing 1H-pyrrolo[2,3-b]pyridine **94** with an appropriate substituted 1H-pyrrolo[2,3-b]pyridine. Azaindoles were purchased or prepared as described in Examples 9 or 16. The following compounds were made following this procedure:

3-[2,6-Dichloro-3-(4-chloro-benzyloxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (**P-1768**),
[2,6-Dichloro-3-(4-chloro-benzyloxy)-phenyl]-(1H-pyrrolo[2,3- b]pyridin-3-yl) methanone (**P-1769**),
(3-Benzoyloxy-2,6-difluoro-phenyl)-(1H-pyrrolo[2,3- b]pyridin-3-yl)-methanone (**P-1802**),
3-(3-Benzoyloxy-2,6-difluoro-benzyl)-1H-pyrrolo[2,3- b]pyridine (**P-1803**),
3-(3-Benzoyloxy-2,6-difluoro-benzyl)-5-methoxy-1H-pyrrolo[2,3- b]pyridine (**P-1804**),
3-(3-Benzoyloxy-2,6-difluoro-benzyl)-5-chloro-1H-pyrrolo[2,3- b]pyridine (**P-1824**),
(3-Benzoyloxy-2,6-difluoro-phenyl)-(5-chloro-1H-pyrrolo[2,3- b]pyridin-3-yl)-methanone (**P-1825**),
3-[(3-Benzoyloxy-2-chloro-6-fluoro-phenyl)-methoxy-methyl]-1H-pyrrolo[2,3- b]pyridine (**P-1867**),
(3-Benzoyloxy-2-chloro-6-fluoro-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**P-1868**),
[2-Chloro-3-(3-chloro-benzyloxy)-6-fluoro-phenyl]-(1H-pyrrolo[2,3- b]pyridin-3-yl)-methanone (**P-1869**),

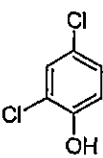
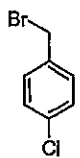
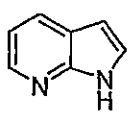
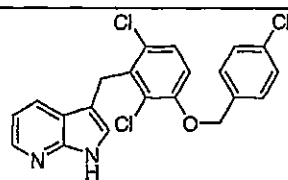
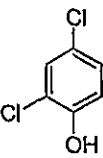
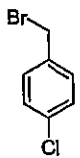
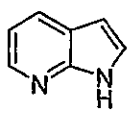
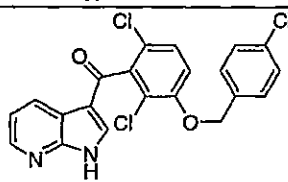
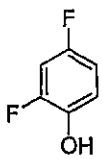
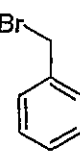
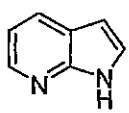
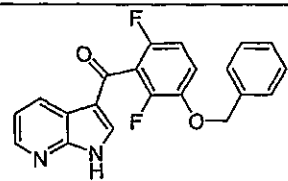
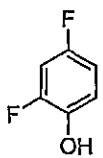
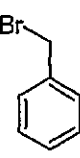
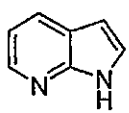
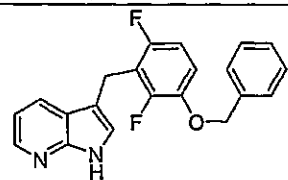
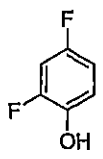
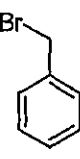
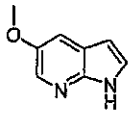
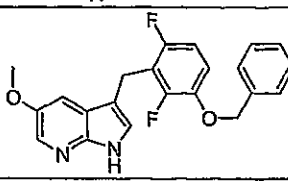
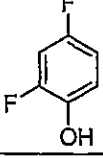
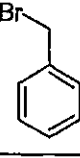
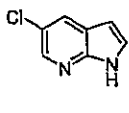
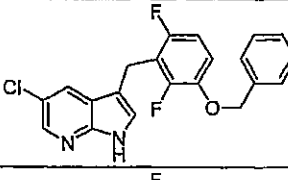
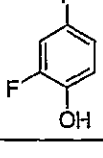
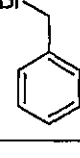
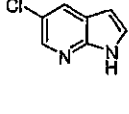
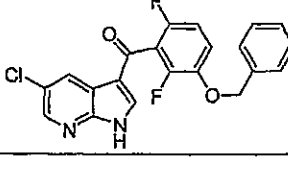
[2-Chloro-3-(4-chloro-benzyloxy)-6-fluoro-phenyl]-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)-methanone (**P-1874**),

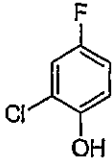
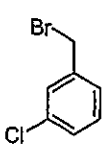
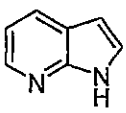
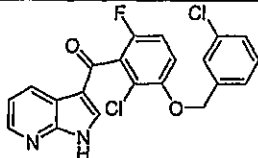
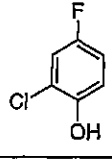
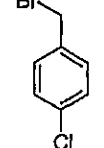
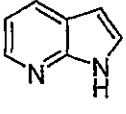
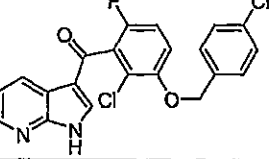
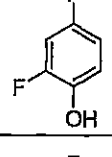
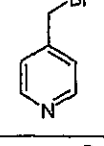
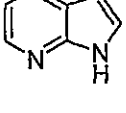
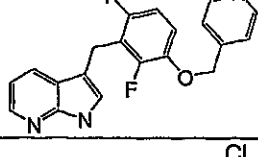
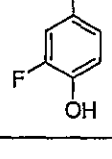
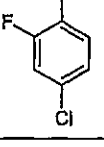
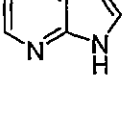
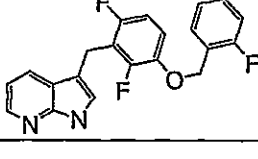
3-[2,6-Difluoro-3-(pyridin-4-ylmethoxy)-benzyl]-1H-pyrrolo[2,3-*b*]pyridine (**P-1993**), and

3-[3-(4-Chloro-2-fluoro-benzyloxy)-2,6-difluoro-benzyl]-1H-pyrrolo[2,3-*b*]pyridine (**P-1992**).

The phenol, benzyl bromide and azaindole used in Steps 1, 2, and 3, respectively, are indicated in columns 2, 3, and 4 of the following table, respectively, to afford the target compound (column 5).

The compound number is provided in column 1, and the observed mass is given in column 6.

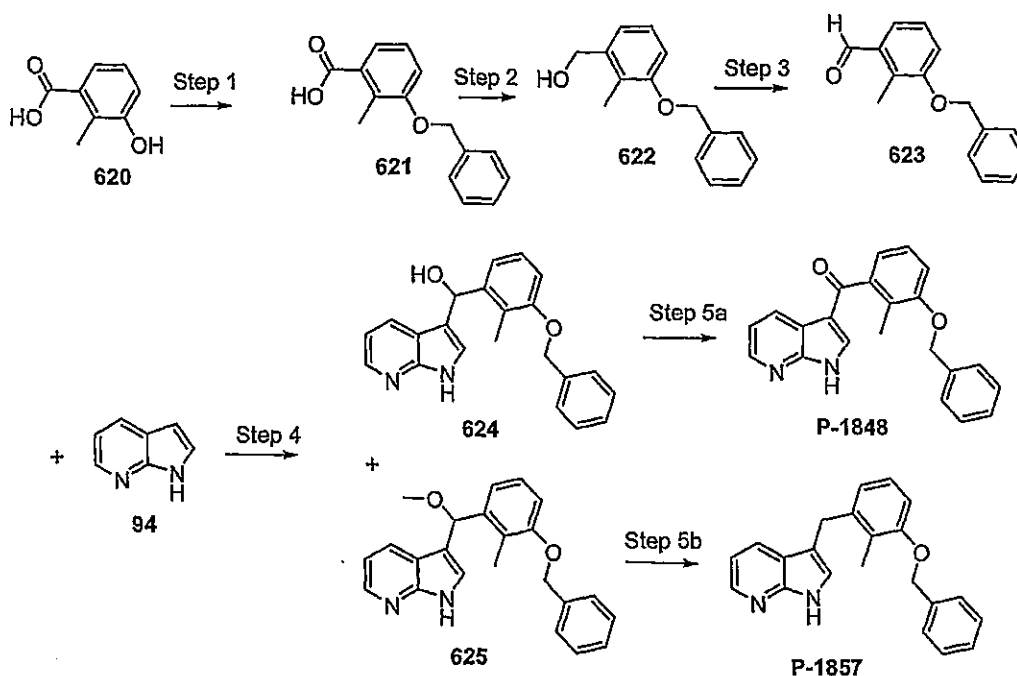
	Phenol	Benzyl bromide	Azaindole	Compound	MS (ESI) $[M+H]^+$ observed
P-1768					417.14
P-1769					431.09
P-1802					365.23
P-1803					351.23
P-1804					381.26
P-1824					385.22
P-1825					399.21

	Phenol	Benzyl bromide	Azaindole	Compound	MS (ESI) $[M+H]^+$ observed
P-1869					415.24
P-1874					415.23
P-1993					352.39
P-1992					403.32

Example 42: Synthesis of (3-Benzoyloxy-2-methyl-phenyl)-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)-methanone P-1848 and 3-(3-Benzoyloxy-2-methyl-benzyl)-1H-pyrrolo[2,3-*b*]pyridine P-1857

[0422] Compounds P-1848 and P-1857 were synthesized in five steps from compounds 620 and 1H-pyrrolo[2,3-*b*]pyridine 94 as shown in Scheme 70.

Scheme 70



Step 1 – Preparation of 3-Benzyloxy-2-methyl-benzoic acid (621):

[0423] To a solution of 3-hydroxy-2-methyl-benzoic acid (620, 5.0 g, 0.033 mol) in tetrahydrofuran (100 mL) and N,N-dimethylformamide (50 mL), sodium hydride (4.4 g as 60% dispersion in mineral oil, 0.11 mol) was added slowly over 30 minutes and the reaction was stirred at 0 °C under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature, then stirred at room temperature for 1 hour. Benzyl bromide (9.0 mL, 0.076 mol) was added slowly into the reaction mixture, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into water, extracted with ethyl acetate, 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 a white solid (621, 5.8 g, 73%).

Step 2 – Preparation of (3-Benzyloxy-2-methyl-phenyl)-methanol (622):

[0424] To a solution of 3-benzyloxy-2-methyl-benzoic acid (621, 3.0 g, 0.012 mol) in tetrahydrofuran (100 mL), lithium aluminum hydride (25 mL, 1M solution in tetrahydrofuran, 0.025 mol) was added dropwise at 0 °C for 5 minutes. The reaction mixture was then stirred at room temperature overnight under an atmosphere of nitrogen. After sodium sulfate decahydrate (20.0 g, 0.062 mol) was added, the reaction mixture was stirred at room temperature for 10 minutes. A white solid was collected by filtration. The solid compound was further washed with a mixture of hexane and dichloromethane (9:1) and dried under high-vacuum (622, 2.8 g, 91%).

Step 3 – Preparation of 3-Benzyloxy-2-methyl-benzaldehyde (623):

[0425] To a solution of (3-benzyloxy-2-methyl-phenyl)-methanol (**622**, 627 mg, 2.75 mmol) in tetrahydrofuran (60 mL) was added Dess-Martin periodinane (2.9 g, 6.87 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 50 minutes. The reaction mixture was quenched with a solution of saturated sodium thiosulfate, extracted with ethyl acetate, washed with sodium bicarbonate, 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 a white solid (**623**, 0.55 g, 84%).

Step 4 – Preparation of (3-Benzyloxy-2-methyl-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (624) and 3-[(3-Benzyloxy-2-methyl-phenyl)-methoxy-methyl]-1H-pyrrolo[2,3-b]pyridine (625):

[0426] A mixture of 1H-pyrrolo[2,3-b]pyridine (**94**, 0.33 g, 2.8 mmol), 3-benzyloxy-2-methyl-benzaldehyde (**623**, 0.55 g, 2.4 mmol), and potassium hydroxide (0.39 g, 6.1 mmol) in methanol (40 mL) was stirred at room temperature for 17 hours. The reaction mixture was poured into water and then extracted with ethyl acetate. The organic layer was collected, 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 hexane to provide compound **624** as an off-white solid (330 mg, 39%, MS(ESI) $[M+H]^+ = 345.29$, and compound **625** as a white solid (24 mg, 3%, MS(ESI) $[M+H]^+ = 359.30$).

Step 5a – Preparation of (3-Benzyloxy-2-methyl-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1848):

[0427] To a solution of (3-Benzyloxy-2-methyl-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**624**, 0.12g, 0.35 mmol) in tetrahydrofuran (15 mL) was added Dess-Martin periodinane (0.37 g, 0.89 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 50 minutes, then quenched with a saturated solution of sodium thiosulfate, extracted with ethyl acetate, washed with sodium bicarbonate, brine, and dried over magnesium sulfate. After removal of solvent, the residue was washed with a mixture of ethyl ether and hexanes (1:1) to provide the compound as a yellow solid (**P-1848**, 108 mg, 90%). MS(ESI) $[M+H]^+ = 343.22$.

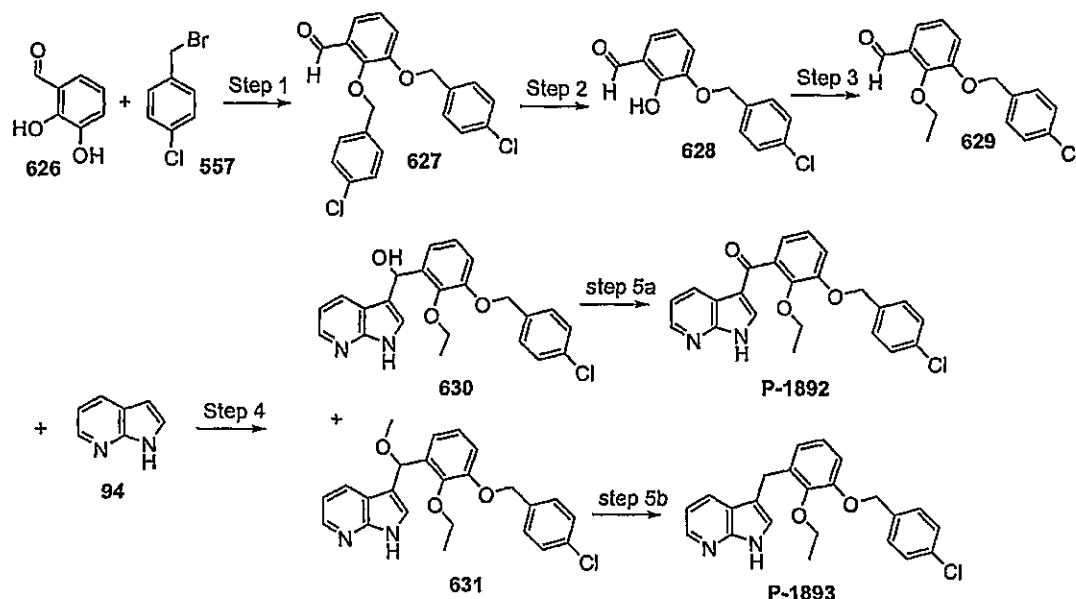
Step 5b – Preparation of 3-(3-Benzyloxy-2-methyl-benzyl)-1H-pyrrolo[2,3-b]pyridine (P-1857):

[0428] A mixture of 3-[(3-benzyloxy-2-methyl-phenyl)-methoxy-methyl]-1H-pyrrolo[2,3-b]pyridine (**625**, 24 mg, 0.067 mmol), trifluoroacetic acid (1 mL, 13 mmol), and triethylsilane (2 mL, 12.5 mmol) in acetonitrile (10 mL) was refluxed for 4 hours. The mixture was concentrated and the residue was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate, brine, and dried over sodium sulfate. After removal of solvent, the residue was washed with a mixture of ethyl ether and hexanes (1:1) to provide the compound as a yellow solid (**P-1857**, 17 mg, 75%). MS(ESI) $[M+H]^+ = 329.24$.

Example 43: Synthesis of [3-(4-chloro-benzyloxy)-2-ethoxy-phenyl]-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)-methanone P-1892 and 3-[3-(4-chloro-benzyloxy)-2-ethoxy-benzyl]-1H-pyrrolo[2,3-*b*]pyridine P-1893

[0429] Compounds P-1892 and P-1893 were synthesized in five steps from compounds 626, 557 and 1H-pyrrolo[2,3-*b*]pyridine 94 as shown in Scheme 71.

Scheme 71



Step 1 – Preparation of 2,3-Bis-(4-chloro-benzyloxy)-benzaldehyde (627):

[0430] To a solution of 2,3-dihydroxybenzaldehyde (626, 2.0 g, 14.5 mmol) in tetrahydrofuran (100 mL) was added sodium hydride (0.52 g, 13.0 mmol) at 0 °C under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 30 minutes. To the reaction mixture was then added 4-chlorobenzyl bromide (557, 2.7 g, 13.0 mmol). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen overnight. N, N-dimethylformamide (50 mL) was added into the reaction mixture and it was stirred at room temperature for 24 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was collected, washed with 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 (627, 2.3 gm, 46%).

Step 2 – Preparation of 3-(4-chloro-benzyloxy)-2-hydroxy-benzaldehyde (628):

[0431] To magnesium (0.098 g, turnings, 4.0 mmol) in a mixture of anhydrous ether (20 mL) and benzene (20 mL) at 0 °C, bromine (0.10 mL, 2.0 mmol) was added dropwise. When the reaction had started, stirring was commenced and the addition of bromine continued until complete. The ice bath

was removed and the reaction mixture was heated until the solution was almost colorless. After cooling down, the reaction mixture was slowly added to a solution of 2, 3-bis-(4-chloro-benzyloxy)-benzaldehyde (**627**, 0.78 g, 2.0 mmol) in benzene (60 mL) at room temperature while stirring vigorously. Upon completion of the addition, the reaction mixture was stirred at room temperature overnight, then refluxed for 36 hours. After the reaction mixture was cooled down to room temperature, a solid was collected by filtration and washed with benzene, then boiled in hydrochloric acid (100 mL, 1.0 M) for 30 minutes. After cool down, the solution was extracted with dichloromethane. The organic layer was washed with brine and dried over magnesium sulfate. An off-white solid was obtained after removal of the solvent (**628**, 0.32 mg, 60%). MS(ESI) [M-H]⁻ = 261.25.

Step 3 – Preparation of 3-(4-chloro-benzyloxy)-2-ethoxy-benzaldehyde (629):

[0432] To a mixture of 3-(4-chloro-benzyloxy)-2-hydroxy-benzaldehyde (110 mg, 0.42 mmol), potassium carbonate (150 mg, 1.1 mmol) in acetonitrile (8 mL) was added iodoethane (0.2 mL, 2.5 mmol) at room temperature. The mixture was stirred at 98 °C for 18 hours. The reaction mixture was poured into a solution of saturated ammonium chloride and was extracted with ethyl acetate. The organic layer was collected, washed with brine, and dried over magnesium sulfate. After removal of solvent, a light yellow solid was obtained (**629**, 116 mg, 95%).

Step 4 – Preparation of [3-(4-chloro-benzyloxy)-2-ethoxy-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (630) and 3-{[3-(4-chloro-benzyloxy)-2-ethoxy-phenyl]-methoxy-methyl}-1H-pyrrolo[2,3-b]pyridine (631):

[0433] A mixture of 1H-Pyrrolo[2,3-b]pyridine (**94**, 26 mg, 0.22 mmol), 3-(4-chloro-benzyloxy)-2-ethoxy-benzaldehyde (**629**, 54 mg, 0.19 mmol), and potassium hydroxide (30 mg, 0.46 mmol) in methanol (5 mL) was stirred at room temperature for 4 days. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was collected, 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 hexane to provide compound **630** as an off-white solid (20 mg, 26%, MS(ESI) [M+H]⁺ = 409.32) and compound **631** as an off-white solid (44 mg, 56%, MS(ESI) [M+H]⁺ = 423.33).

Step 5a – Preparation of [3-(4-chloro-benzyloxy)-2-ethoxy-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1892):

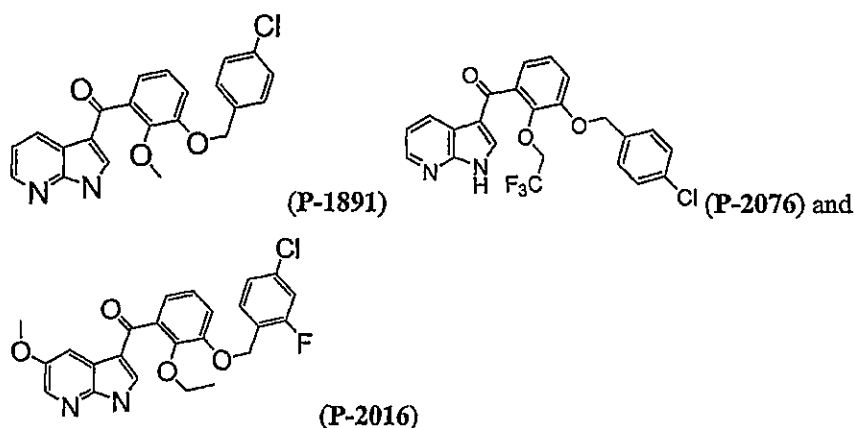
[0434] To a solution of [3-(4-chloro-benzyloxy)-2-ethoxy-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**630**, 20 mg, 0.05 mmol) in tetrahydrofuran (8 mL) was added Dess-Martin periodinane (52 mg, 0.12 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 50 minutes. The reaction was quenched with a saturated solution of sodium thiosulfate, extracted with ethyl acetate, washed with sodium bicarbonate, brine, and dried over magnesium sulfate. After removal of solvent, the residue

was washed with a mixture of ethyl ether and hexanes (1:1) to provide the compound as a yellow solid (**P-1892**, 15 mg, 75%). MS(ESI) $[M+H]^+ = 407.38$.

Step 5b – Preparation of 3-[3-(4-chloro-benzyloxy)-2-ethoxy-phenyl]-1H-pyrrolo[2,3-b]pyridine (P-1893):

[0435] A mixture of 3-[[3-(4-chloro-benzyloxy)-2-ethoxy-phenyl]-methoxy-methyl]-1H-pyrrolo[2,3-b]pyridine (**631**, 44 mg, 0.1 mmol), trifluoroacetic acid (1 mL, 13 mmol), and triethylsilane (2 mL, 12.5 mmol) in acetonitrile (10 mL) was refluxed for 4 hours. The mixture was concentrated and the residue was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate, brine, and dried over sodium sulfate. After removal of solvent, the residue was washed with a mixture of ethyl ether and hexanes (1:1) to provide the compound as a yellow solid (**P-1893**, 40 mg, 98%). MS(ESI) $[M+H]^+ = 393.39$.

[0436] [3-(4-Chloro-benzyloxy)-2-methoxy-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-1891**), [3-(4-chloro-benzyloxy)-2-(2,2,2-trifluoroethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2076**), and [3-(4-chloro-2-fluoro-benzyloxy)-2-ethoxy-phenyl]-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2016**)

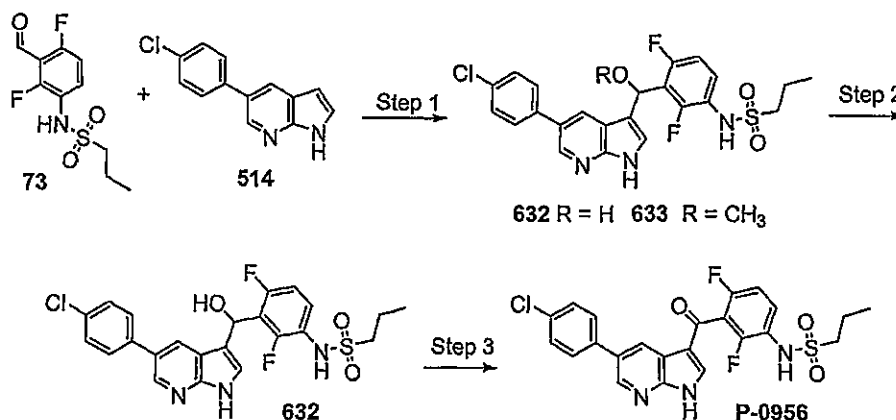


were prepared following the protocol of Scheme 71, substituting iodoethane with iodomethane in step 3 to provide **P-1891**, or substituting iodoethane with 2-iodo-1,1,1-trifluoroethane in step 3 to provide **P-2076**, or substituting 4-chlorobenzyl bromide **557** with 4-chloro-2-fluoro-benzyl bromide in step 1 and 7-azaindole **94** with 5-methoxy-7-azaindole in step 4 to provide **P-2016**. MS(ESI) $[M+H]^+ = 393.4$ (**P-1891**), 461.08 (**P-2076**), and 455.2 (**P-2016**).

Example 44. Synthesis of Propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide P-0956

[0437] Compound **P-0956** was synthesized in three steps from 5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine **514** and propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide **73** as shown in Scheme 72.

Scheme 72



Step 1-Preparation of Propane-1-sulfonic acid (3-[[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-hydroxy-methyl]-2,4-difluoro-phenyl)-amide (632) and Propane-1-sulfonic acid (3-[[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methoxy-methyl]-2,4-difluoro-phenyl)-amide (633):

[0438] To a suspension of 5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine (514, 64.9 g, 158 mM, prepared as described in Example 17) and propane-1-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (73, 90.4 g, 191 mM, prepared as described in Example 7) in methanol in a water bath was added potassium hydroxide (128.8 g, 1.28 M). The reaction was stirred 72 hours at room temperature and then adjusted to pH 7 with 4N hydrochloric acid. The resulting mixture was evaporated *in vacuo* to remove methanol and extracted 3x with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated *in vacuo* to give a crude oil. The crude oil was triturated with 3:1 MTBE/heptane to give a 1:3 solid mixture of 632 and 633 that was used directly for the next step.

Step 2-Preparation of Propane-1-sulfonic acid (3-[[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-hydroxy-methyl]-2,4-difluoro-phenyl)-amide (632):

[0439] To a solution of 632 and 633 (ca. 315 mM) in acetic acid was added 48% hydrobromic acid (final 8%). The resulting mixture was stirred overnight at room temperature and then evaporated *in vacuo*. The crude residue was taken up with equal volumes of ethyl acetate and water, and adjusted to pH 7 with solid potassium carbonate. The layers were split and the aqueous layer was extracted 2x with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated *in vacuo* to give 632 as a viscous oil that was used directly for the next step.

Step 3-Preparation of Propane-1-sulfonic acid (3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl)-amide (P-0956):

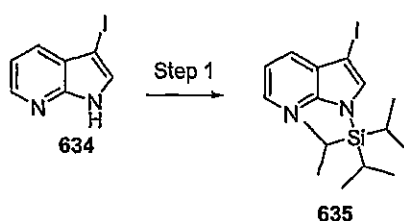
[0440] To a solution of 632 (ca. 386 mM) in 1,4-dioxane was added 2,3-dichloro-5,6-dicyanobenzoquinone (83.8 g, 502 mM) followed by water (final 4.8%). The resulting mixture was stirred 2 hours at room temperature and then quenched with one volume of saturated sodium bicarbonate. The mixture was evaporated *in vacuo* to remove 1,4-dioxane and extracted 3x with ethyl

acetate. The combined organic layers were dried over sodium sulfate and evaporated *in vacuo* to give a crude solid that was purified on a silica-gel column with 94:5:1 dichloromethane/methanol/ammonium hydroxide as eluent to give **P-0956** (approximately 50% yield for 3 steps) as a white solid.

Example 45: Synthesis of 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine 635

[0441] 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine **635** was synthesized in one step from 3-Iodo-1H-pyrrolo[2,3-b]pyridine **634** as shown in Scheme 73.

Scheme 73



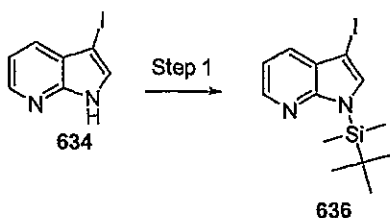
Step 1 – Preparation of 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (635):

[0442] 3-Iodo-1H-pyrrolo[2,3-b]pyridine **634** (2.00 g, 8.20 mmol) was dissolved in N,N-dimethylformamide (50 mL). Sodium hydride (60% dispersion in mineral oil, 390 mg, 9.8 mmol) was added. After 20 minutes, triisopropylsilyl chloride (1.74 mL, 8.20 mmol) was added dropwise. After 1.5 hours, the reaction was poured into water and extracted with ethyl acetate, washed with saturated sodium bicarbonate and brine. The organic portions were dried over anhydrous sodium sulfate and concentrated. Purification by silica gel chromatography, 0-25% gradient ethyl acetate/hexane gave compound **635** as a white solid (3.224 g, 98.2%). ¹H-NMR was consistent with the desired compound,

Example 46: Synthesis of 1-(tert-Butyl-dimethyl-silanyl)-3-iodo-1H-pyrrolo[2,3-b]pyridine 636

[0443] 1-(tert-Butyl-dimethyl-silanyl)-3-iodo-1H-pyrrolo[2,3-b]pyridine **636** was synthesized in one step from 3-Iodo-1H-pyrrolo[2,3-b]pyridine **634** as shown in Scheme 74.

Scheme 74

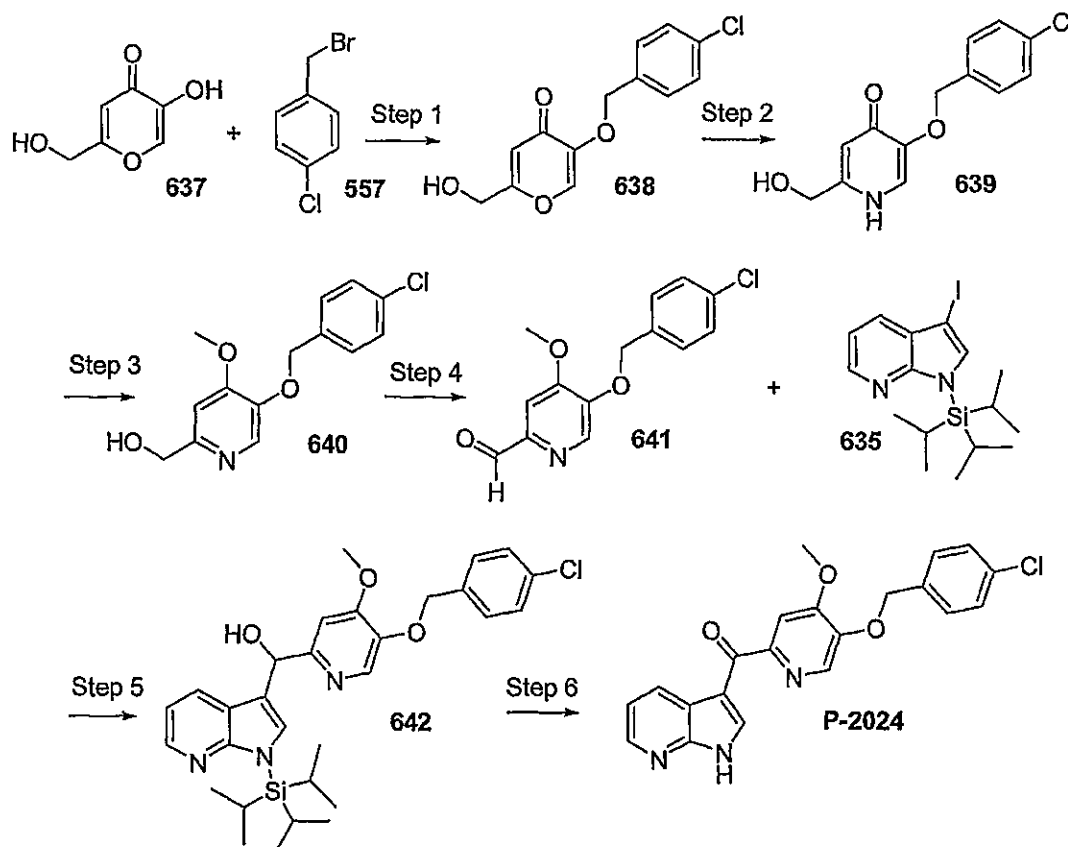


Step 1 – Preparation of 1-(tert-Butyl-dimethyl-silanyl)-3-iodo-1H-pyrrolo[2,3-b]pyridine (636):

[0444] 3-Iodo-1H-pyrrolo[2,3-b]pyridine 634 (1.11 g, 4.6 mmol) was dissolved in tetrahydrofuran (120 mL). Sodium hydride (60% dispersion in mineral oil, 0.13 g, 5.5 mmol) was added, followed by tert-butyldimethylsilyl chloride (0.85 g, 5.5 mmol). The reaction was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate. The organic portion was washed with brine, 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 compound as a white solid (636, 100 mg, 15%).

Example 47: Synthesis of [5-(4-chloro-benzyloxy)-4-methoxy-pyridin-2-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-2024

[0445] [5-(4-Chloro-benzyloxy)-4-methoxy-pyridin-2-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-2024 was synthesized in six steps from Kojic acid, 3, and 3-iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine, 2, as shown in Scheme 75.

Scheme 75*Step 1 – Preparation of 5-(4-chloro-benzyloxy)-2-hydroxymethyl-pyran-4-one (638):*

[0446] Kojic acid (637, 5.00 g, 35.2 mmol) and 4-chlorobenzyl bromide (557, 7.95 g, 38.7 mmol)

were suspended in methanol (40 mL) in an 80 mL sealed tube. Sodium hydroxide in water (12 M, 2.93 mL) was added. The reaction was heated at 80 °C overnight. The resulting suspension was concentrated. Water was added and the mixture was filtered and washed with water to provide a brown solid. Washing with minimal methanol on the filter removed the brown color. A white solid (638, 7.58 g, 80%) was isolated. ¹H-NMR was consistent with the desired compound.

Step 2 – Preparation of 5-(4-chloro-benzyloxy)-2-hydroxymethyl-1H-pyridin-4-one (639):

[0447] 5-(4-Chloro-benzyloxy)-2-hydroxymethyl-pyran-4-one (638, 8.00 g, 3.00 mmol) was suspended in ammonium hydroxide (200 mL) in an 80 mL sealed tube. The reaction was heated at 90 °C overnight. Upon cooling, the reaction was lowered to pH 10 with 6N HCl to provide a beige solid that was collected by filtration (639, 7.8 g, 98%).

Step 3 – Preparation of [5-(4-chloro-benzyloxy)-4-methoxy-pyridin-2-yl]-methanol (640):

[0448] 5-(4-Chloro-benzyloxy)-2-hydroxymethyl-1H-pyridin-4-one (639, 1.06 g, 3.99 mmol) was dissolved in methanol (8.5 mL) and N,N-dimethylformamide (46 mL). Trimethylsilyldiazomethane in hexane (2.00 M, 3.99 mL) was added. The reaction was stirred at room temperature overnight, then additional trimethylsilyldiazomethane in hexane (2.00 M, 3.99 mL) was added. The reaction was stirred at room temperature for 2 days. The mixture was adsorbed onto silica and purified by silica gel chromatography, methanol:dichloromethane to provide the compound (640, 798 mg, 72 %). MS(ESI) [M+H]⁺ = 280.4, 282.4.

Step 4 – Preparation of 5-(4-chloro-benzyloxy)-4-methoxy-pyridine-2-carbaldehyde (641):

[0449] [5-(4-Chloro-benzyloxy)-4-methoxy-pyridin-2-yl]-methanol (640, 480 mg, 1.7 mmol) was dissolved in dimethyl sulfoxide (26 mL) and Dess-Martin periodinane (909 mg, 2.1 mmol) was added. The reaction was allowed to stir at room temperature for 2 hours. The reaction was concentrated under high vacuum and then poured into a solution of NaHCO₃ and Na₂S₂O₃. The mixture was extracted with ethyl acetate. The organic portions were dried with anhydrous sodium sulfate and filtered. The filtrate was adsorbed onto silica and purified by silica gel chromatography, ethyl acetate:hexanes, to provide the desired compound as a white powder (641, 343 mg, 72 %).

Step 5 – Preparation of [5-(4-chloro-benzyloxy)-4-methoxy-pyridin-2-yl]-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (642):

[0450] 3-Iodo-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (635, 180 mg, 0.450 mmol) was dissolved in tetrahydrofuran (2.5 mL) and the reaction was cooled to -20 °C under an atmosphere of nitrogen. Isopropylmagnesium chloride in tetrahydrofuran (2.00 M, 0.243 mL) was added. The reaction was stirred for 1 hour, during which the temperature rose to 0 °C. The reaction was cooled to -20 °C and 5-(4-chloro-benzyloxy)-4-methoxy-pyridine-2-carbaldehyde (641, 80.0 mg, 0.288 mmol) in tetrahydrofuran (0.75 mL) was added. The reaction was allowed to warm to room temperature and

stirred overnight. The reaction was quenched with methanol and adsorbed onto silica, then purified by silica gel chromatography, methanol: dichloromethane, to provide the desired product, (**642**, 94 mg, 59%). $^1\text{H-NMR}$ was consistent with the desired compound. MS(ESI) $[\text{M}+\text{H}]^+ = 552.4, 554.4, 555.4$.

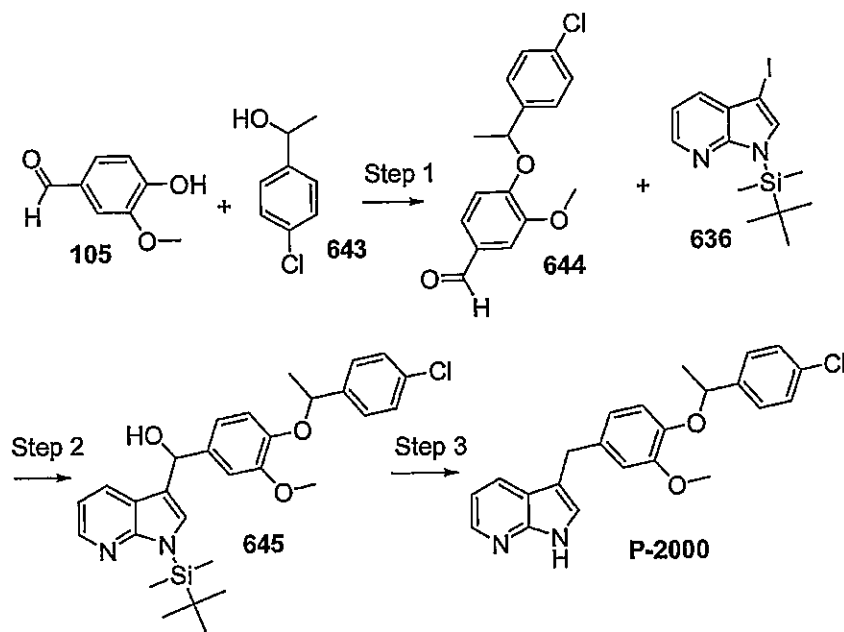
Step 6— Preparation of [5-(4-chloro-benzyloxy)-4-methoxy-pyridin-2-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-2024):

[0451] [5-(4-Chloro-benzyloxy)-4-methoxy-pyridin-2-yl]-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**642**, 60.0 mg, 0.11 mmol) was dissolved in tetrahydrofuran (2.00 mL). Dess-Martin periodinane (55.3 mg, 0.13 mmol) was added to the reaction and it was stirred at room temperature overnight. The mixture was extracted with ethyl acetate and saturated sodium bicarbonate. The organic portions were dried with anhydrous sodium sulfate, filtered and the filtrate was adsorbed onto silica and purified by silica gel chromatography, methanol:dichloromethane, to provide the desired compound (**P-2024**, 10.7 mg, 25%). $^1\text{H-NMR}$ was consistent with the desired compound. MS(ESI) $[\text{M}+\text{H}]^+ = 394.1, 396.1$.

Example 48: Synthesis of 3-4-[1-(4-chloro-phenyl)-ethoxy]-3-methoxy-benzyl-1H-pyrrolo[2,3-b]pyridine P-2000

[0452] 3-4-[1-(4-Chloro-phenyl)-ethoxy]-3-methoxy-benzyl-1H-pyrrolo[2,3-b]pyridine **P-2000** was synthesized in three steps from vanillin **105**, 4-chlorophenylmethylcarbinol **643**, and 1-(tert-butyl-dimethyl-silyl)-3-iodo-1H-pyrrolo[2,3-b]pyridine **636**, as shown in Scheme 76.

Scheme 76



Step 1 – Preparation of 4-[1-(4-chloro-phenyl)-ethoxy]-3-methoxy-benzaldehyde (644):

[0453] 4-Chlorophenylmethylethanol (643, 0.668 mL, 6.57 mmol) was dissolved in tetrahydrofuran (60.0 mL) at 0 °C under an atmosphere of nitrogen. 4-Hydroxy-3-methoxybenzaldehyde (105, 1.00 g, 6.57 mmol) and triphenylphosphine (2.07 g, 7.89 mmol) were added to the reaction, followed by diisopropyl azodicarboxylate (1.55 mL, 7.89 mmol) over 10 minutes. The reaction was stirred for 2 hours. The mixture was adsorbed onto silica and purified by silica gel chromatography, ethyl acetate:hexanes, to provide the desired compound, (644, 1.14 g, 60 %). ¹H-NMR was consistent with the desired compound.

Step 2 – Preparation of [1-(tert-Butyl-dimethyl-silanyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-4-[1-(4-chloro-phenyl)-ethoxy]-3-methoxy-phenyl-methanol (645):

[0454] 1-(tert-Butyl-dimethyl-silanyl)-3-iodo-1H-pyrrolo[2,3-b]pyridine (636, 647.0 mg, 1.81 mmol) was dissolved in tetrahydrofuran (10.0 mL) at -20 °C under an atmosphere of nitrogen. Isopropylmagnesium chloride in tetrahydrofuran (2.0 M, 0.98 mL) was added to the reaction. The reaction was stirred for 1 hour, during which the temperature rose to 0 °C. The reaction was cooled to -20 °C and 4-[1-(4-chloro-phenyl)-ethoxy]-3-methoxy-benzaldehyde (644, 420 mg, 1.4 mmol) in tetrahydrofuran (3.00 mL) was added. The reaction was stirred for 2 hours during which time the temperature rose to 10 °C. The reaction was quenched with methanol and adsorbed onto silica, then purified by silica gel chromatography, ethyl acetate:hexanes, to provide the desired compound, (645, 463 mg, 61%). ¹H-NMR was consistent with the desired compound.

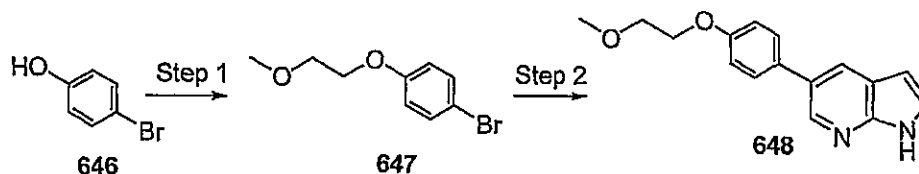
Step 2 – Preparation of 3-4-[1-(4-chloro-phenyl)-ethoxy]-3-methoxy-benzyl-1H-pyrrolo[2,3-b]pyridine (P-2000):

[0455] [1-(tert-Butyl-dimethyl-silanyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-4-[1-(4-chloro-phenyl)-ethoxy]-3-methoxy-phenyl-methanol (645, 0.200 g, 0.382 mmol) was dissolved in acetonitrile (5.00 mL). Trifluoroacetic acid (0.138 mL) was added and the reaction was stirred for five minutes. Triethylsilane (0.285 mL) was added and the reaction was heated at 80 °C for 2 hours. The reaction was concentrated, then redissolved in ethyl acetate and adsorbed onto silica and purified by silica gel chromatography, ethyl acetate:hexanes, to provide the desired compound (P-2000, 57 mg, 38 %). ¹H-NMR was consistent with the desired compound. MS(ESI): [M+H]⁺ = 393.3, 395.3.

Example 49: Synthesis of 5-[4-(2-methoxyethoxy)-phenyl]-1H-pyrrolo[2,3-b]pyridine 648

[0456] 5-[4-(2-Methoxyethoxy)-phenyl]-1H-pyrrolo[2,3-b]pyridine 648 was synthesized in two steps from 4-bromophenol 646 as shown in Scheme 77.

Scheme 77



Step 1 – Preparation 1-Bromo-4-(2-methoxy-ethoxy)-benzene (647):

[0457] To a solution of 4-bromophenol (646, 5.0 g, 28.9 mmol) in dimethylformamide (15 mL) were added potassium carbonate (4.40 g, 31.8 mmol) and 1-bromo-2-methoxyethane (5.00 g, 36.0 mmol) under an atmosphere of nitrogen. The reaction mixture was stirred at ambient temperature overnight and concentrated under reduced pressure. The residue was slurried in ethyl acetate (50 mL) and filtered. The filtrate was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate and filtered. Silica gel column chromatography (0-10% ethyl acetate in hexanes) gave the desired compound as a colorless oil (647, 3.2 g, 48%).

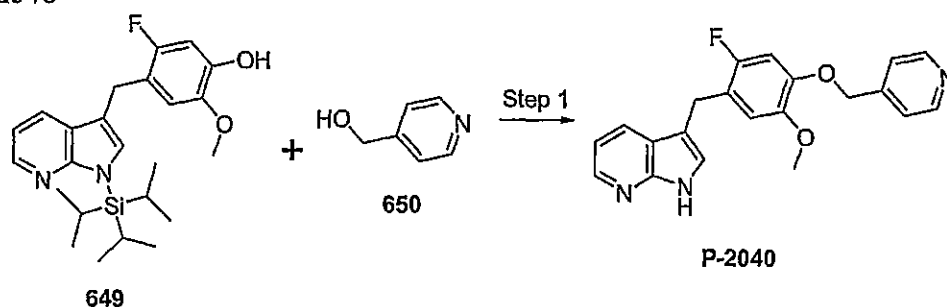
Step 2 – Preparation of 5-[4-(2-Methoxy-ethoxy)-phenyl]-1H-pyrrolo[2,3-b]pyridine (648):

[0458] To a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (1.1 g, 4.3 mmol) in tetrahydrofuran (40 mL) was added 1-bromo-4-(2-methoxy-ethoxy)-benzene (647, 1.50 g, 6.49 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.25 g, 0.21 mmol). The reaction mixture was stirred with potassium carbonate solution (10 mL, 1.0 M) and warmed to reflux overnight. The biphasic reaction mixture was diluted with ethyl acetate (50 mL) and saturated sodium carbonate solution (20 mL). The organic layer was separated, washed with brine, dried over magnesium sulfate and purified by silica gel column chromatography (50-100% ethyl acetate in hexanes) to give the desired compound as a colorless solid (648, 782 mg, 67%). MS (ESI) $[M+H]^+ = 267.4$.

Example 50: Synthesis of 3-[2-fluoro-5-methoxy-4-(pyridin-4-ylmethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine P-2040 and related compounds.

[0459] Compound P-2040 was synthesized in one step from 5-fluoro-2-methoxy-4-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenol 649 and pyridin-4-yl-methanol 650 as shown in Scheme 78.

Scheme 78



Step 1 – Preparation of 3-[2-fluoro-5-methoxy-4-(pyridin-4-ylmethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2040):

[0460] 5-Fluoro-2-methoxy-4-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-ylmethyl)-phenol (649, 10 mg, 0.024 mmol, prepared as described in Example 57) was combined with pyridin-4-yl-methanol (650, 3.2mg, 0.029 mmol) in a 4 mL vial and dissolved in dry tetrahydrofuran (200μl). Triphenylphosphine (7.7 mg) was added and the solution was shaken until homogenous. The mixture was cooled to below 0 °C in a liquid nitrogen bath and diisopropyl azodicarboxylate solution (50μl of 20mg/50μl in THF) was added. The reaction mixture was allowed to warm to room temperature. After 2 hours, the solvent was removed under reduced atmosphere. The crude material was dissolved in dimethyl sulfoxide (300μl) and potassium fluoride (10 mg, 0.18mmol) was added. The mixture was heated gently and allowed to react overnight at room temperature. The vial was centrifuged and the DMSO solution was purified by reverse phase HPLC using a YMC-Pack ODS-A C-18 column (50mm x 10mm ID), and eluting with water with 0.1% TFA and a gradient of 15%-80% acetonitrile with 0.1% TFA over 8 minutes and a flow rate of 6 mL/minute to provide the compound (P-2040, 4.4 mg, 50%). MS (ESI) $[M+H]^+ = 364.3$.

[0461] Additional compounds were prepared following the protocol of Scheme 78, replacing pyridin-4-yl-methanol 650 with an appropriate alcohol. The following compounds were made following this procedure:

- 3-[2-Fluoro-5-methoxy-4-(2-morpholin-4-yl-ethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2037),
- 3-[2-Fluoro-5-methoxy-4-(pyridin-3-ylmethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2038),
- 3-[2-Fluoro-5-methoxy-4-(6-methyl-pyridin-2-ylmethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2039),
- 3-[2-Fluoro-5-methoxy-4-(pyridin-2-ylmethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2041),
- 3-[2-Fluoro-4-(2-fluoro-4-trifluoromethyl-benzyloxy)-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2042),
- 3-[4-(4-Chloro-2-fluoro-benzyloxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-1973),

3-[4-(2,4-Dimethyl-thiazol-5-ylmethoxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2043),

3-[4-(2,5-Dimethyl-2H-pyrazol-3-ylmethoxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2044),

3-[2-Fluoro-5-methoxy-4-(3-morpholin-4-yl-propoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2045),

1-{2-[5-Fluoro-2-methoxy-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenoxy]-ethyl}-pyrrolidin-2-one (P-2046),

3-[2-Fluoro-4-(2-fluoro-benzyloxy)-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2047),

3-[2-Fluoro-5-methoxy-4-(3-methyl-pyridin-4-ylmethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2048),

3-[2-Fluoro-5-methoxy-4-(6-trifluoromethyl-pyridin-3-ylmethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2049),

3-[4-(2,4-Dichloro-benzyloxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2050),

3-[2-Fluoro-4-(4-imidazol-1-yl-benzyloxy)-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2051),

3-[4-(2,4-Difluoro-benzyloxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2052),

3-{2-Fluoro-4-[1-(2-fluoro-phenyl)-ethoxy]-5-methoxy-benzyl}-1H-pyrrolo[2,3-b]pyridine (P-2053),

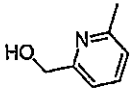
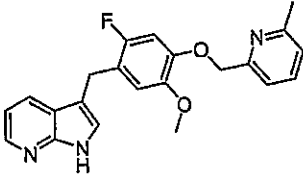
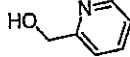
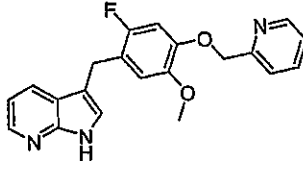
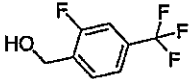
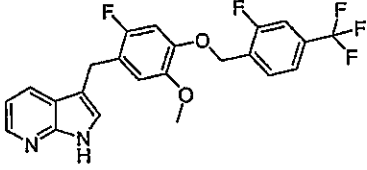
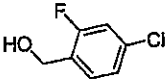
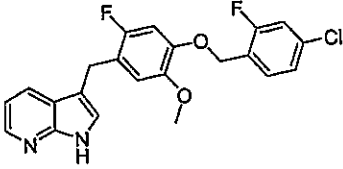
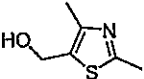
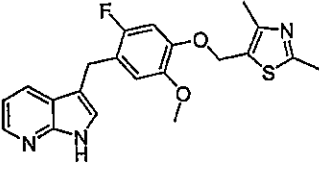
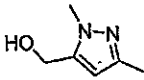
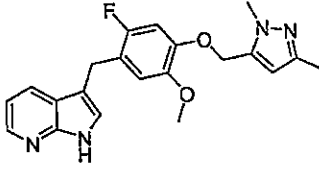
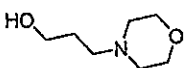
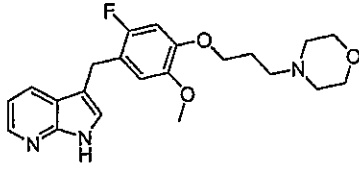
3-[4-(3-Cyclopentyl-propoxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2054),

3-[4-(1,5-Dimethyl-1H-pyrazol-3-ylmethoxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2055), and

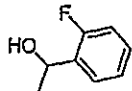
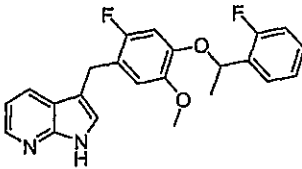
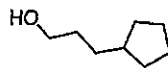
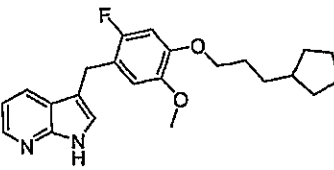
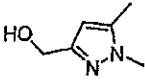
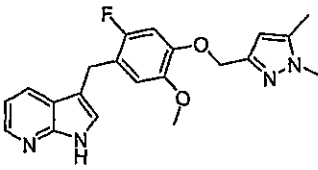
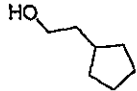
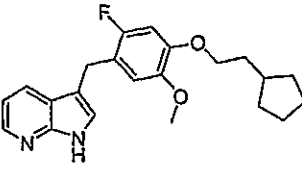
3-[4-(2-Cyclopentyl-ethoxy)-2-fluoro-5-methoxy-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2056)

The following table indicates the alcohol (column 2) used in Scheme 78 to provide the compounds (column 4). Column 1 provides the compound number and column 4 the observed mass.

	Alcohol	Compound	MS(ESI) [M+H] ⁺ observed
P-2037			386.3
P-2038			364.3

	Alcohol	Compound	MS(ESI) [M+H] ⁺ observed
P-2039			378.3
P-2041			364.3
P-2042			448.7
P-1973			415.1
P-2043			397.9
P-2044			381.1
P-2045			400.3

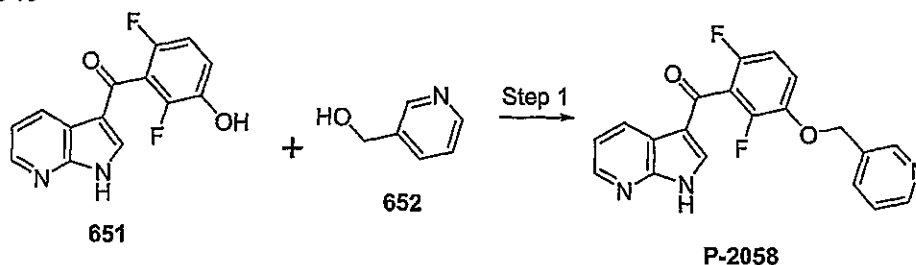
	Alcohol	Compound	MS(ESI) [M+H] ⁺ observed
P-2046			384.3
P-2047			381.1
P-2048			378.3
P-2049			432.3
P-2050			431.1
P-2051			429.1
P-2052			399.1

	Alcohol	Compound	MS(EST) [M+H] ⁺ observed
P-2053			395.1
P-2054			383.1
P-2055			381.1
P-2056			369.1

Example 51: Synthesis of [2,6-difluoro-3-(pyridin-3-ylmethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-2058 and related compounds.

[0462] Compound P-2058 was synthesized in 1 step from (2,6-Difluoro-3-hydroxy-phenyl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **651** and Pyridin-3-yl-methanol **652** as shown in Scheme 79.

Scheme 79



Step 1 – Preparation of [2,6-Difluoro-3-(pyridin-3-ylmethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-2058):

[0463] In a 4mL vial, (2,6-Difluoro-3-hydroxy-phenyl)-(1H-pyrrolo[2,3-b]pyridine-3-yl)-methanone (651, 10 mg, 0.037 mmol, prepared as described in Example 23) was combined with pyridin-3-yl-methanol (652, 4.9 mg 0.044 mmol). The solids were dissolved in dry tetrahydrofuran (200µl) and triphenylphosphine (11.5 mg, 0.044 mmol) was added. Once the solution was homogenous, the mixture was cooled to below 0 °C in liquid nitrogen bath and diisopropyl azodicarboxylate solution (50µl of 20mg/50µl THF) was added. The reaction mixture was allowed to warm to room temperature and the reaction was continued for 2 hours. The solvents were removed under reduced atmosphere. The resultant residue was diluted with 200µl DMSO and the mixture purified by reverse phase HPLC using a YMC-Pack ODS-A C-18 column (50mm x 10mm ID), and eluting with water with 0.1% TFA and a gradient of 15%-80% acetonitrile with 0.1% TFA over 8 minutes and a flow rate of 6 mL/minute to provide **P-2058** (5.9 mg, 44 %). MS (ESI) $[M+H]^+ = 365.9$.

[0464] Additional compounds were prepared following the protocol of Scheme 79, replacing pyridin-3-yl-methanol 652 with an appropriate alcohol. The following compounds were made following this procedure:

[2,6-Difluoro-3-(1-methyl-1H-imidazol-2-ylmethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2033**),

[2,6-Difluoro-3-(6-morpholin-4-yl-pyridin-3-ylmethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2034**),

{2,6-Difluoro-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzyloxy]-phenyl}-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2035**),

[3-(6-Diethylamino-pyridin-3-ylmethoxy)-2,6-difluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2036**),

[3-(2-Chloro-4-fluoro-benzyloxy)-2,6-difluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2057**),

[2,6-Difluoro-3-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2059**),

[2,6-Difluoro-3-(pyridin-4-ylmethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2060**),

[3-(4-Chloro-2-fluoro-benzyloxy)-2,6-difluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2061**),

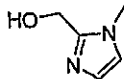
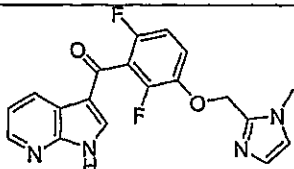
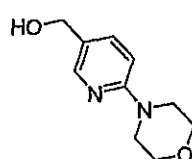
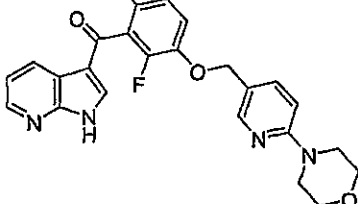
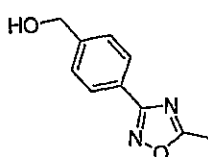
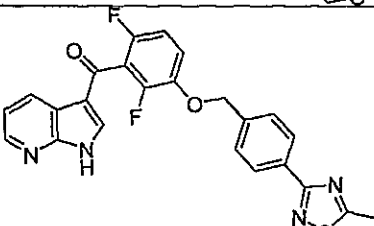
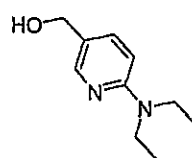
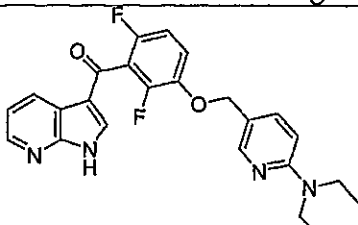
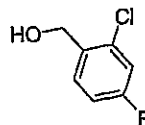
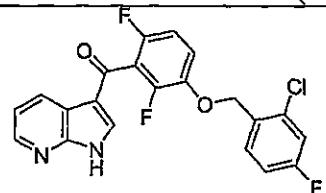
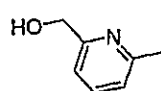
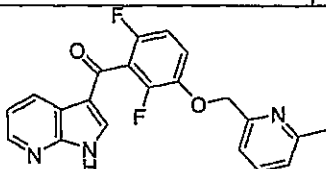
[3-(2,4-Dimethyl-thiazol-5-ylmethoxy)-2,6-difluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2062**),

[3-(2,5-Dimethyl-2H-pyrazol-3-ylmethoxy)-2,6-difluoro-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2063**), and

[2,6-Difluoro-3-(3-morpholin-4-yl-propoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2064**).

The following table indicates the alcohol (column 2) used to afford the compound (column 3).

Column 1 provides the compound number and column 4 the observed mass.

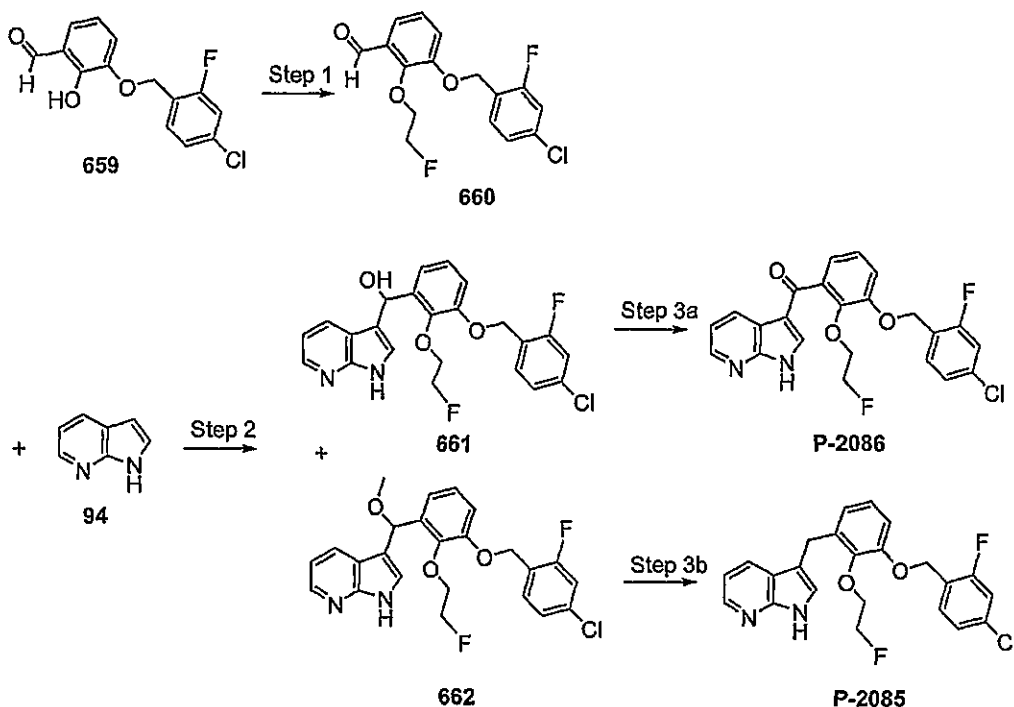
	Alcohol	Compound	MS(ESI) [M+H] ⁺ observed
P-2033			369.1
P-2034			451.1
P-2035			447.1
P-2036			437.1
P-2057			417.1
P-2059			380.3

	Alcohol	Compound	MS(ESI) [M+H] ⁺ observed
P-2060			365.9
P-2061			417.1
P-2062			399.9
P-2063			383.1
P-2064			402.3

Example 52: Synthesis of [3-(4-Chloro-2-fluoro-benzyloxy)-2-(2-fluoro-ethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-2086 and 3-[3-(4-Chloro-2-fluoro-benzyloxy)-2-(2-fluoro-ethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine P-2085

[0465] Compounds P-2086 and P-2085 were synthesized in three steps from compounds 659 and 1H-pyrrolo[2,3-b]pyridine 94 as shown in Scheme 81.

Scheme 81



Step 1 – Preparation of 3-(4-Chloro-2-fluoro-benzyloxy)-2-(2-fluoro-ethoxy)-benzaldehyde (660):

[0466] To a solution of 3-(4-Chloro-2-fluoro-benzyloxy)-2-hydroxy-benzaldehyde (659, 140 mg, 0.5 mmol), prepared by protocol of Example 43, Steps 1 and 2 of Scheme 71, using 4-chloro-2-fluoro-benzyl bromide in place of 4-chloro-benzyl bromide in Step 1) in tetrahydrofuran (8 mL) was added dropwise a mixture of 2-fluoro-ethanol (64 mg, 1.0 mmol), triphenylphosphine (180 mg, 0.7 mmol), and diisopropyl azodicarboxylate (120 mg, 0.6 mol) in tetrahydrofuran (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes and then at 40 °C for 3 days. The reaction mixture was dissolved in water and ethyl acetate. The organic layers were collected, washed with brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexanes to provide the compound as a white solid (660, 88 mg, 54%). MS (ESI) $[M+H]^+ = 327.12$.

Step 2 – Preparation of [3-(4-Chloro-2-fluoro-benzyloxy)-2-(2-fluoro-ethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (661) and 3-[[3-(4-Chloro-2-fluoro-benzyloxy)-2-(2-fluoro-ethoxy)-phenyl]-methoxy-methyl]-1H-pyrrolo[2,3-b]pyridine (662):

[0467] A solution of 3-(4-chloro-2-fluoro-benzyloxy)-2-(2-fluoro-ethoxy)-benzaldehyde (660, 88 mg, 0.27 mmol), 1H-pyrrolo[2,3-b]pyridine (94, 38 mg, 0.32 mmol), and potassium hydroxide (45 mg, 0.81 mol) in methanol (5 mL) was stirred at room temperature for 24 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was collected, 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 hexane to provide compound **661** as a white solid (67 mg, 56%), MS(ESI) $[M+H]^+ = 445.13$ and compound **662** as a white solid (36 mg, 29%), MS(ESI) $[M+H]^+ = 459.15$.

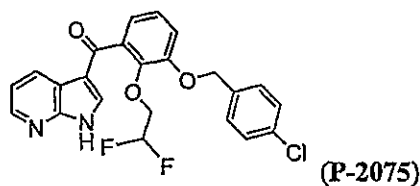
Step 3a – Preparation of [3-(4-Chloro-2-fluoro-benzyloxy)-2-(2-fluoro-ethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-2086):

[0468] To a solution of [3-(4-chloro-2-fluoro-benzyloxy)-2-(2-fluoro-ethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**661**, 60 mg, 0.1 mmol) in tetrahydrofuran (10 mL) was added Dess-Martin periodinane (69 mg, 0.16 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 hours. The reaction was quenched with a saturated solution of sodium thiosulfate, extracted with ethyl acetate, washed with sodium bicarbonate, brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexanes to provide the compound as a white solid (**P-2086**, 15 mg, 20%). MS(ESI) $[M+H]^+ = 441.06$.

Step 3b – Preparation of 3-[3-(4-Chloro-2-fluoro-benzyloxy)-2-(2-fluoro-ethoxy)-benzyl]-1H-pyrrolo[2,3-b]pyridine (P-2085):

[0469] A mixture of 3-[[3-(4-chloro-2-fluoro-benzyloxy)-2-(2-fluoro-ethoxy)-phenyl]-methoxy-methyl]-1H-pyrrolo[2,3-b]pyridine (**662**, 36 mg, 0.078 mmol), triethylsilane (0.5 mL, 3 mmol), and trifluoroacetic acid (0.2 mL, 2 mmol) in acetonitrile (20 mL) was stirred at 80 °C for 2 hours. The mixture was concentrated and the residue was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate, 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 compound as a yellow solid (**P-2085**, 24 mg, 71%). MS(ESI) $[M+H]^+ = 429.15$.

[0470] 3-(4-Chloro-benzyloxy)-2-(2,2-difluoro-ethoxy)-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-2075**)

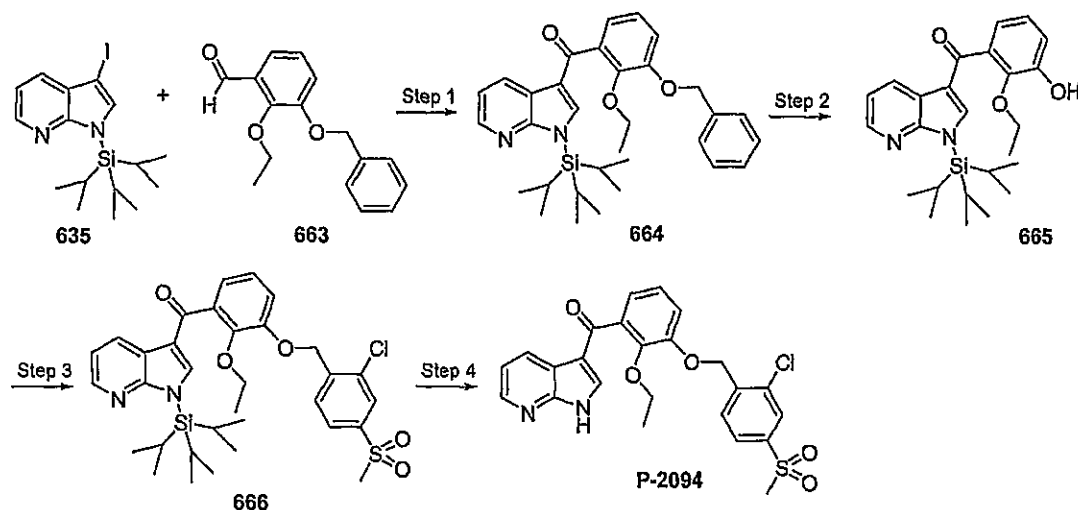


was prepared following the protocol of Scheme 81, substituting 2-fluoro-ethanol with 2,2-difluoro-ethanol and substituting 3-(4-Chloro-2-fluoro-benzyloxy)-2-hydroxy-benzaldehyde with 3-(4-chloro-benzyloxy)-2-hydroxy-benzaldehyde (**628** of Example 43) in Step 1 to provide **P-2075**. MS(ESI) $[M+H]^+ = 443.1$.

Example 53: Synthesis of [3-(2-Chloro-4-methanesulfonyl-benzyloxy)-2-ethoxy-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-2094

[0471] Compound P-2094 was synthesized in four steps from compounds 635 and 663 as shown in Scheme 82.

Scheme 82



Step 1 – Preparation of (3-Benzyloxy-2-ethoxy-phenyl)-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (664):

[0472] To a solution of 3-iodo-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (635, 1.306 g, 3.26 mmol) in tetrahydrofuran (42 mL) at -20 °C under nitrogen was added isopropylmagnesium chloride (1.70 mL, 2.0 M solution in tetrahydrofuran, 3.40 mmol). The reaction mixture was stirred at -20 °C for 1.5 hours. It was allowed to warm to 5 °C and then kept at 5 °C for 1 hour. The reaction mixture was then cooled down to -20 °C. To this solution was slowly added a solution of 2-ethoxy-3-benzyloxybenzaldehyde (663, 0.698 g, 2.72 mmol, prepared by protocol of Example 43, Steps 1-3 of Scheme 71, using benzyl bromide in place of 4-chloro-benzyl bromide in Step 1) in tetrahydrofuran (42 mL). The reaction mixture was stirred at -20 °C for 2.5 hrs, and was allowed to warm to 5 °C for 2.5 hours. The reaction mixture was poured into iced water, extracted with ethyl acetate, washed with saturated ammonium chloride and 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 light-yellow oil (664, 200 mg, 13.9%).

Step 2 – Preparation of (2-ethoxy-3-hydroxy-phenyl)-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (665):

[0473] To a solution of (3-benzyloxy-2-ethoxy-phenyl)-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (664, 195 mg, 0.37 mmol) in a mixture of methanol (20 mL) and tetrahydrofuran (50 mL) was added palladium on carbon (50 mg, 10% wt., 0.2 mmol). The mixture was stirred under hydrogenation for seventeen hours. After removal of solvent, the residue was

washed with a mixture of ethyl ether and hexanes to provide the compound as a white solid (665, 63 mg, 95%). MS(ESI) $[M+H]^+ = 439.37$.

Step 3 – Preparation of [3-(2-Chloro-4-methanesulfonyl-benzyloxy)-2-ethoxy-phenyl]-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (666):

[0474] To a solution of (2-ethoxy-3-hydroxy-phenyl)-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (665, 40 mg, 0.064 mmol) in tetrahydrofuran (15 mL) was added sodium hydride (3.32 mg, 0.083 mmol) at room temperature under an atmosphere of nitrogen. The mixture was stirred at room temperature for 40 minutes, then 1-bromomethyl-2-chloro-4-methanesulfonyl-benzene (21.72 mg, 0.077 mmol) was added to the reaction mixture. It was stirred at room temperature overnight. The mixture was then poured into water and was extracted with ethyl acetate. The organic layer was collected and washed with brine, dried over magnesium sulfate. After removal of the solvent, a crude compound as light yellow oil was obtained (666, 84 mg).

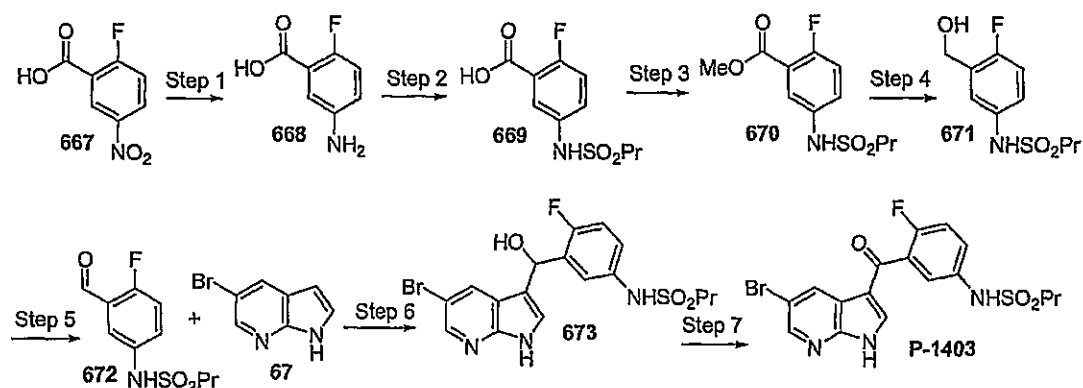
Step 4 – Preparation of [3-(2-Chloro-4-methanesulfonyl-benzyloxy)-2-ethoxy-phenyl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-2094):

[0475] To a solution of (2-ethoxy-3-hydroxy-phenyl)-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (666, 84 mg, 0.054 mmol) in methanol (10 mL) was added potassium hydroxide (6 N solution) until pH of the solution turned to over 10. Potassium fluoride (30 mg, 0.5 mmol) was then added to the reaction mixture and the mixture was stirred at room temperature for 6 hours. The reaction mixture was then poured into saturated sodium carbonate and was extracted with ethyl acetate. The organic layer was collected and washed with brine, dried over magnesium sulfate. After removal of the solvent, the residue was purified by preparative HPLC to provide as a white solid (P-2094, 5 mg, 19%). MS(ESI) $[M+H]^+ = 485.17$.

Example 54: Synthesis of Propane-1-sulfonic acid [3-(5-bromo -1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-fluoro-phenyl]-amide P-1403

[0476] Compound P-1403 was synthesized in seven steps from 3-fluoro-5-nitrobenzoic acid 667 as shown in Scheme 83.

Scheme 83



Step 1 – Preparation of 3-fluoro-5-aminobenzoic acid (668):

[0477] Into a Parr pressure reactor were added 3-fluoro-5-nitrobenzoic acid (667, 5.0 g, 0.027 mol), methanol (50.0 mL), 20% Pd(OH)₂ on carbon (300 mg). The reaction was shaken under an atmosphere of hydrogen at 50 psi overnight. The reaction was filtered through celite and was concentrated to dryness to provide a white solid (668, 4.0 g, 95.0%).

Step 2 – Preparation of 2-Fluoro-5-(propane-1-sulfonylamino)-benzoic acid (669):

[0478] To 3-fluoro-5-aminobenzoic acid (668, 3.00 g, 0.0180 mol) in methylene chloride (204 mL) were added pyridine (41 mL, 0.50 mol) and propane-1-sulfonyl chloride (2.23 mL, 0.0198 mol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 5 days. The reaction was poured into water, adjusted pH to 1 with 1N HCl, 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% methanol in methylene chloride to give a white solid (669, 2.0 g, 42%). MS (ESI) [M-H]⁺ = 260.1.

Step 3 – Preparation of 2-Fluoro-5-(propane-1-sulfonylamino)-benzoic acid methyl ester (670):

[0479] To 2-Fluoro-5-(propane-1-sulfonylamino)-benzoic acid (669, 2.0 g, 0.0076 mol) in methanol (20.0 mL) was added sulfuric acid (0.90 mL, 0.017 mol). The reaction was stirred at room temperature overnight. The reaction was concentrated and purified with silica gel column chromatograph eluting with 20% ethyl acetate in hexane to give a white solid (670, 1.27 g, 62%). MS (ESI) [M-H]⁺ = 274.1.

Step 4 – Preparation of Propane-1-sulfonic acid (4-fluoro-3-hydroxymethyl-phenyl)-amide (671):

[0480] To 2-Fluoro-5-(propane-1-sulfonylamino)-benzoic acid methyl ester (670, 1.20 g, 0.00436 mol) in tetrahydrofuran (100.0 mL) was added lithium tetrahydroaluminate (1.00 M in tetrahydrofuran, 10.0 mL) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight. To the reaction was added Na₂SO₄·10H₂O (5 g), and then stirred at room temperature for 1 hour. The reaction was filtered, concentrated and purified with silica gel column

chromatography eluting with 50% ethyl acetate in hexane to give the compound (**671**, 0.90 g, 83%). MS (ESI) $[M-H]^+ = 246.1$.

Step 5 – Preparation of Propane-1-sulfonic acid (4-fluoro-3 -formyl-phenyl)-amide (672):

[0481] To propane-1-sulfonic acid (4-fluoro-3 -hydroxymethyl-phenyl)-amide (**671**, 0.483 g, 0.00195 mol) in tetrahydrofuran (10.0 mL), cooled with ice/water, was added Dess-Martin periodinane (1.00 g, 0.00236 mol). The reaction was stirred at 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 concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give a white solid (**672**, 360 mg, 75%). MS (ESI) $[M-H]^+ = 244.1$.

Step 6 – Preparation of Propane-1-sulfonic acid 3-[(5-brom o-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-4-fluoro-phenyl-amide (673):

[0482] To 5-bromo-7-azaindole (**67**, 170.0 mg, 0.86 mmol) in methanol (7.0 mL) were added propane-1-sulfonic acid (4-fluoro-3 -formyl-phenyl)-amide (**672**, 220.0 mg, 0.90 mmol) and potassium hydroxide (0.50 g, 0.0089 mol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight. The reaction was poured into water, acidified with 1N HCl to pH = 5, 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 10% methanol in methylene chloride to give the compound (**673**, 55.0 mg, 14.0%). MS (ESI) $[M+H]^+ = 442.1, 444.1$.

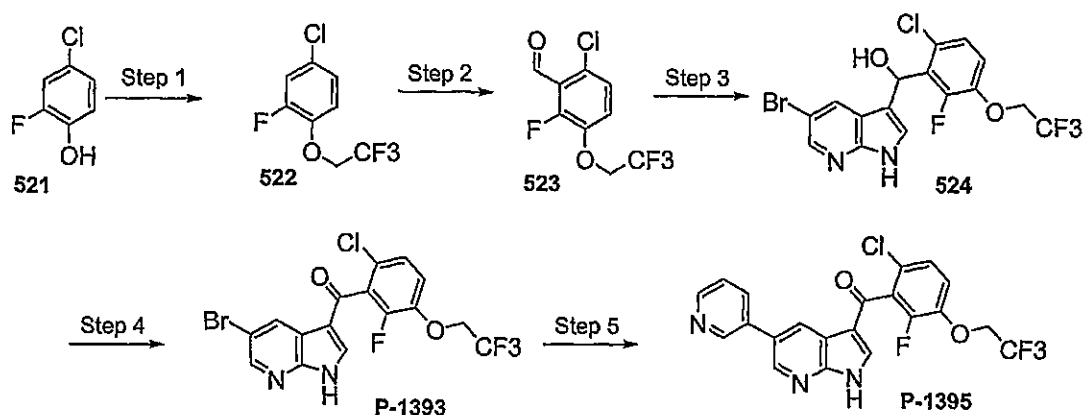
Step 7 – Preparation of Propane-1-sulfonic acid [3-(5-bromo -1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-fluoro-phenyl]-amide (P-1403):

[0483] To propane-1-sulfonic acid 3-[(5-brom o-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-4-fluoro-phenyl-amide (**673**, 55.0 mg, 0.12 mmol) in tetrahydrofuran (8.0 mL) was added Dess-Martin periodinane (70.0 mg, 0.17 mmol). The reaction was stirred at room temperature for 5 minutes. The reaction was concentrated with silica gel and purified with silica gel column chromatography eluting with 25% ethyl acetate in hexane to give an off-white solid (**P-1403**, 26.2 mg, 47%). MS (ESI) $[M+H]^+ = 437.9, 439.9$.

Example 55: Synthesis of 2-[2,4-Difluoro-3-(5-pyridin-3-yl-1 H-pyrrolo[2,3-b]pyridin-3-ylmethyl) -phenoxy]-ethanol P-1395 and related compounds

[0484] Compound **P-1395** was synthesized in four steps from 4-Chloro-2-fluoro-phenol **521** as shown in Scheme 42.

Scheme 42



Step 1 – Preparation of 4-Chloro-2-fluoro-1-(2,2,2-trifluoro-ethoxy)-benzene (522):

[0485] To 4-Chloro-2-fluoro-phenol (**521**, 5.0 g, 0.034 mol) in methanol (50.0 mL) was added potassium fluoride (2.2 g, 0.038 mol). The solvent was removed. The resulting salt was added to N,N-dimethylformaldehyde (25 mL), followed by adding 1,1,1-trifluoro-2-iodo-ethane (8.60 g, 40.9 mmol). The reaction was stirred at 50 °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 20% ethyl acetate in hexane to give colorless oil (**522**, 2.0 g, 26%).

Step 2 – Preparation of 6-Chloro-2-fluoro-3-(2,2,2-trifluoro-ethoxy)-benzaldehyde (523):

[0486] To 4-Chloro-2-fluoro-1-(2,2,2-trifluoro-ethoxy)-benzene (**522**, 0.80 g, 3.5 mmol) in THF (20 mL), cooled in dry ice/acetone bath and under an atmosphere of nitrogen, was slowly added n-butyllithium (1.60 M in Hexane, 2.30 mL). After an hour, N,N-dimethylformamide (0.298 mL, 3.85 mmol) was added to the reaction. After 30 minutes, the reaction was allowed to reach room temperature and was stirred 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 concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give the compound (**523**, 450 mg, 50%).

Step 3 – Preparation of (5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-chloro-2-fluoro-3-(2,2,2-trifluoro-ethoxy)-phenyl]-methanol (524):

[0487] To 5-bromo-7-azaindole (**67**, 291 mg, 1.48 mmol) in methanol (22 mL) were added 6-Chloro-2-fluoro-3-(2,2,2-trifluoro-ethoxy)-benzaldehyde (**523**, 400.0 mg, 1.6 mmol) and potassium hydroxide (1.49 g, 26.6 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 48 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 25% ethyl acetate in hexane to give the compound

(524, 300 mg, 42%). MS (ESI) $[M+H]^+ = 453.1, 455.1$.

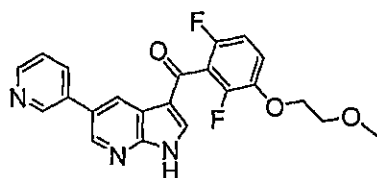
Step 4 – Preparation of (5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-chloro-2-fluoro-3-(2,2,2-trifluoro-ethoxy)-phenyl]-methanol (P-1393):

[0488] To (5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-chloro-2-fluoro-3-(2,2,2-trifluoro-ethoxy)-phenyl]-methanol (524, 140.0 mg, 0.31 mmol) in tetrahydrofuran (6.0 mL) was added Dess-Martin periodinane (157 mg, 0.37 mmol). The reaction was stirred at 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 concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give the compound (P-1393, 100 mg, 72%). MS (ESI) $[M-H]^- = 448.9, 450.9$.

Step 5 – Preparation of [6-Chloro-2-fluoro-3-(2,2,2-trifluoro-ethoxy)-phenyl]-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-1395):

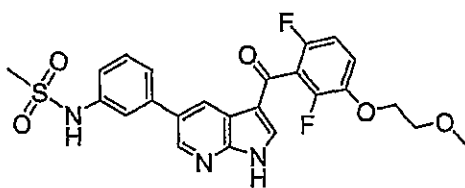
[0489] To (5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-chloro-2-fluoro-3-(2,2,2-trifluoro-ethoxy)-phenyl]-methanol (P-1393, 53.0 mg, 0.12 mmol) in acetonitrile (4.0 mL) was added Tetrakis(triphenylphosphine)palladium(0) (5.0 mg, 0.0043 mmol), 3-pyridylboronic acid (15.1 mg, 0.12 mmol) and 1 M potassium carbonate solution (1.5 mL). The reaction was microwaved (300 watts) at 160 °C for 7 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 concentrated and purified by silica gel column chromatography eluting with 60% ethyl acetate in hexane to give the compound (P-1395, 3.8 mg, 53%) as light yellow solid. MS (ESI) $[M+H]^+ = 450.2$.

[0490] [2,6-Difluoro-3-(2-methoxy-ethoxy)-phenyl]-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-1456



was prepared following the protocol of Scheme 42, substituting 4-Chloro-2-fluoro-phenol 521 with 2,4-difluoro-phenol and 1,1,1-Trifluoro-2-iodo-ethane with 1-Bromo-2-methoxy-ethane in Step 1. MS (ESI) $[M + H]^+ = 410.2$.

[0491] N-(3-{3-[2,6-Difluoro-3-(2-methoxy-ethoxy)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-phenyl)-methanesulfonamide P-1472

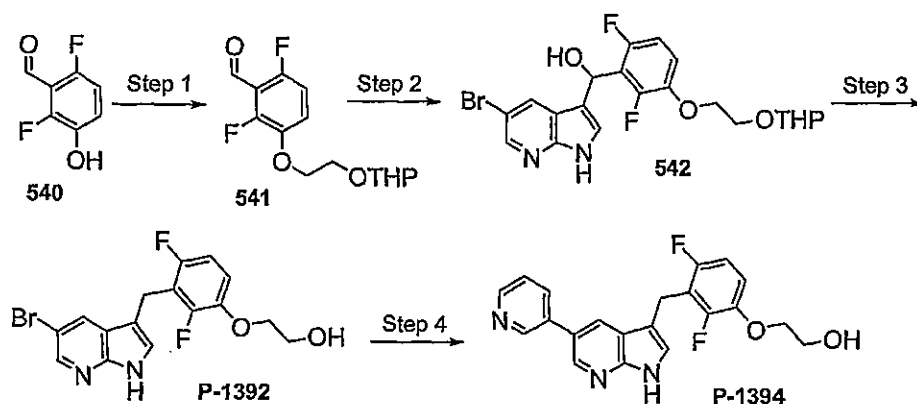


was prepared following the protocol of Scheme 42, substituting 4-Chloro-2-fluoro-phenol **521** with 2,4-difluoro-phenol and 1,1,1-Trifluoro-2-iodo-ethane with 1-Bromo-2-methoxy-ethane in Step 1, and substituting pyridine-3-boronic acid with [(3-methylsulfonyl)aminophenyl]-boronic acid in step 4. MS (ESI) $[M + H]^+ = 502.2$.

Example 56: Synthesis of 2-[2,4-Difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl) -phenoxy]-ethanol P-1394

[0492] Compound **P-1394** was synthesized in four steps from 2,6-Difluoro-3-hydroxy-benzaldehyde **540** as shown in Scheme 48.

Scheme 48



Step 1 – Preparation of 2,6-Difluoro-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-benzaldehyde (541):

[0493] To 2,6-difluoro-3-hydroxy-benzaldehyde (**540**, 0.150 g, 0.95 mmol) in N,N-dimethylformamide (8.0 mL) were added 2-(2-bromo-ethoxy)-tetrahydro-pyran (0.218 g, 1.04 mmol) and potassium carbonate (0.52 g, 3.8 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature 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 purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give the compound as colorless oil (**541**, 180 mg, 66%).

Step 2 – Preparation of (5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-2,6-difluoro-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl-methanol (542):

[0494] To 5-bromo-7-azaindole (**67**, 118 mg, 0.000597 mol) in methanol (9.0 mL) were added 2,6-

difluoro-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-benzaldehyde (**541**, 180.0 mg, 0.63 mmol) and potassium hydroxide (601.9 mg, 10.7 mmol) 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 to give crude compound that was used directly in the next step.

Step 3 – Preparation of 2-[3-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenoxy]-ethanol (P-1392):

[0495] To (5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-2,6-difluoro-3-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl-methanol (**542**, 0.22 g, 0.46 mmol) in acetonitrile (6.0 mL) were added trifluoroacetic acid (0.14 mL, 1.8 mmol) and triethylsilane (0.29 mL, 1.8 mmol). The reaction was stirred at room temperature overnight. The filtrate was concentrated and purified by silica gel column chromatography eluting with 35% ethyl acetate in hexane to give the compound as a white solid (**P-1392**, 62 mg, 35%). MS ($M+H^+$)⁺ = 383.1, 385.1.

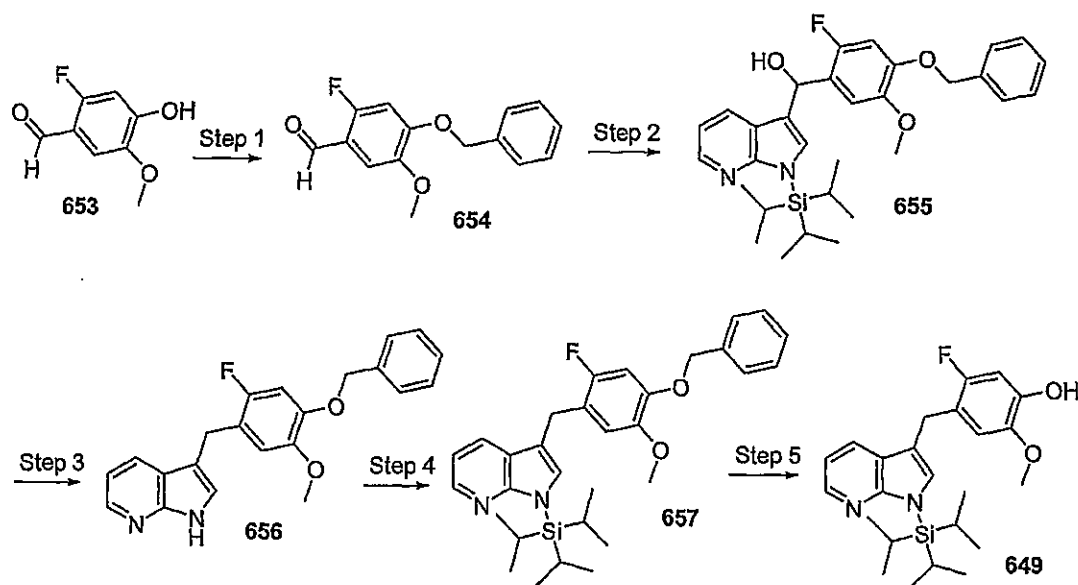
Step 4 – Preparation of 2-[2,4-Difluoro-3-(5-pyridin-3-yl-1 H-pyrrolo[2,3-b]pyridin-3-ylmethyl) -phenoxy]-ethanol (P-1394):

[0496] To 2-[3-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-2,4-difluoro-phenoxy]-ethanol (**P-1392**, 35.0 mg, 0.091 mmol) in acetonitrile (4.0 mL) were added 3-pyridylboronic acid (14.6 mg, 0.12 mmol), tetrakis(triphenylphosphine)palladium(0) (3.0 mg, 0.0026 mmol) and 1 M potassium carbonate solution (1.5 mL). The reaction was microwaved (300 watts) at 160°C for 7 minutes. The reaction was poured into water and extracted with ethyl acetate. The organic layer was collected and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting 4% methanol in methylene chloride to give the compound as white solid (**P-1394**, 11.0 mg, 32%). MS (ESI) [$M+H^+$]⁺ = 382.2.

Example 57: Synthesis of 5-fluoro-2-methoxy-4-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenol 649.

[0497] 5-Fluoro-2-methoxy-4-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenol **649** was synthesized in five steps from 2-fluoro-4-hydroxy-5-methoxy-benzaldehyde **653** and benzyl bromide as shown in Scheme 80.

Scheme 80



Step 1 – Preparation of 4-Benzyloxy-2-fluoro-5-methoxy-benzaldehyde (654):

[0498] 2-Fluoro-4-hydroxy-5-methoxy-benzaldehyde (**653**, 1.62 g, 9.52 mmol) was dissolved in *N,N*-dimethylformamide (50 mL) and sodium hydride (60% dispersion in mineral oil, 530 mg, 13 mmol) was added. After 20 minutes, benzyl bromide (1.5 mL, 12 mmol) was added to the reaction mixture. The reaction was stirred at room temperature under an atmosphere of nitrogen for 5.5 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 0-50 % ethyl acetate in hexane to provide compound as a white solid, consistent with the desired structure by ¹H-NMR (**654**, 2.0 g, 81 %).

Step 2 – Preparation of (4-Benzyloxy-2-fluoro-5-methoxy-phenyl)-(1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (655):

[0499] 3-Iodo-1-triisopropylsilanyl-1H-pyrrolo[2,3-b]pyridine (**635**, 620 mg, 1.5 mmol, prepared as described in Example 45) was dissolved in tetrahydrofuran (15 mL) at -20 °C under an atmosphere of nitrogen. Isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 840 µL) was added to the reaction. The reaction was stirred for 1.5 hours, during which the temperature rose to 5 °C. The reaction was cooled to -20 °C. 4-Benzyloxy-2-fluoro-5-methoxy-benzaldehyde (**654**, 250 mg, 0.9606 mmol) in tetrahydrofuran (5.0 mL) was added to the reaction. The reaction was stirred for 2.5 hours during which time the temperature rose to 5 °C. The reaction was poured into water. The mixture was 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 2-25 % ethyl acetate in hexane to provide compound as a white solid (**655**, 501 mg, 63 %). MS (ESI) $[M+H]^+ = 535.4$.

Step 3 – Preparation of 3-(4-Benzyloxy-2-fluoro-5-methoxy-benzyl)-1H-pyrrolo[2,3-b]pyridine (656):

[0500] (4-Benzyloxy-2-fluoro-5-methoxy-phenyl)-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (**655**, 1.49 g, 2.79 mmol) was dissolved in acetonitrile (50 mL) and trifluoroacetic Acid (1.1 mL) was added. The reaction was stirred for 5 minutes. Triethylsilane (2.2 mL) was added to the reaction. The reaction was heated at 80 °C for 6 hours. The reaction was concentrated and the crude material was dissolved into ethyl acetate and washed with 1 N HCl, saturated sodium bicarbonate, and brine. The organic portion was dried over anhydrous sodium sulfate and concentrated. The solid obtained was used in the next reaction without further purification (**656**, 833 mg, 83%). MS (ESI) $[M+H]^+ = 363.4$.

Step 4 – Preparation of 3-(4-Benzyloxy-2-fluoro-5-methoxy-benzyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (657):

[0501] 3-(4-Benzyloxy-2-fluoro-5-methoxy-benzyl)-1H-pyrrolo[2,3-b]pyridine (**656**, 0.877 g, 2.42 mmol) was dissolved in N,N-dimethylformamide (30 mL). Sodium hydride (60% dispersion in mineral oil, 140 mg, 3.6 mmol) was added at room temperature. After 20 minutes, triisopropylsilyl chloride (513 μ L, 2.42 mmol) was added dropwise. The reaction was stirred for four hours. The reaction was poured into water and extracted with ethyl acetate. The organic portion was washed with saturated sodium bicarbonate and brine. The organic portion was dried over anhydrous sodium sulfate and filtered. The filtrate was adsorbed onto silica gel and purified by silica gel chromatography using 20-80% ethyl acetate/ hexane. The resulting material was purified a second time with 5-30% gradient ethyl acetate/ hexane to provide the desired compound (**657**, 831 mg, 66%). MS (ESI) $[M+H]^+ = 519.4$.

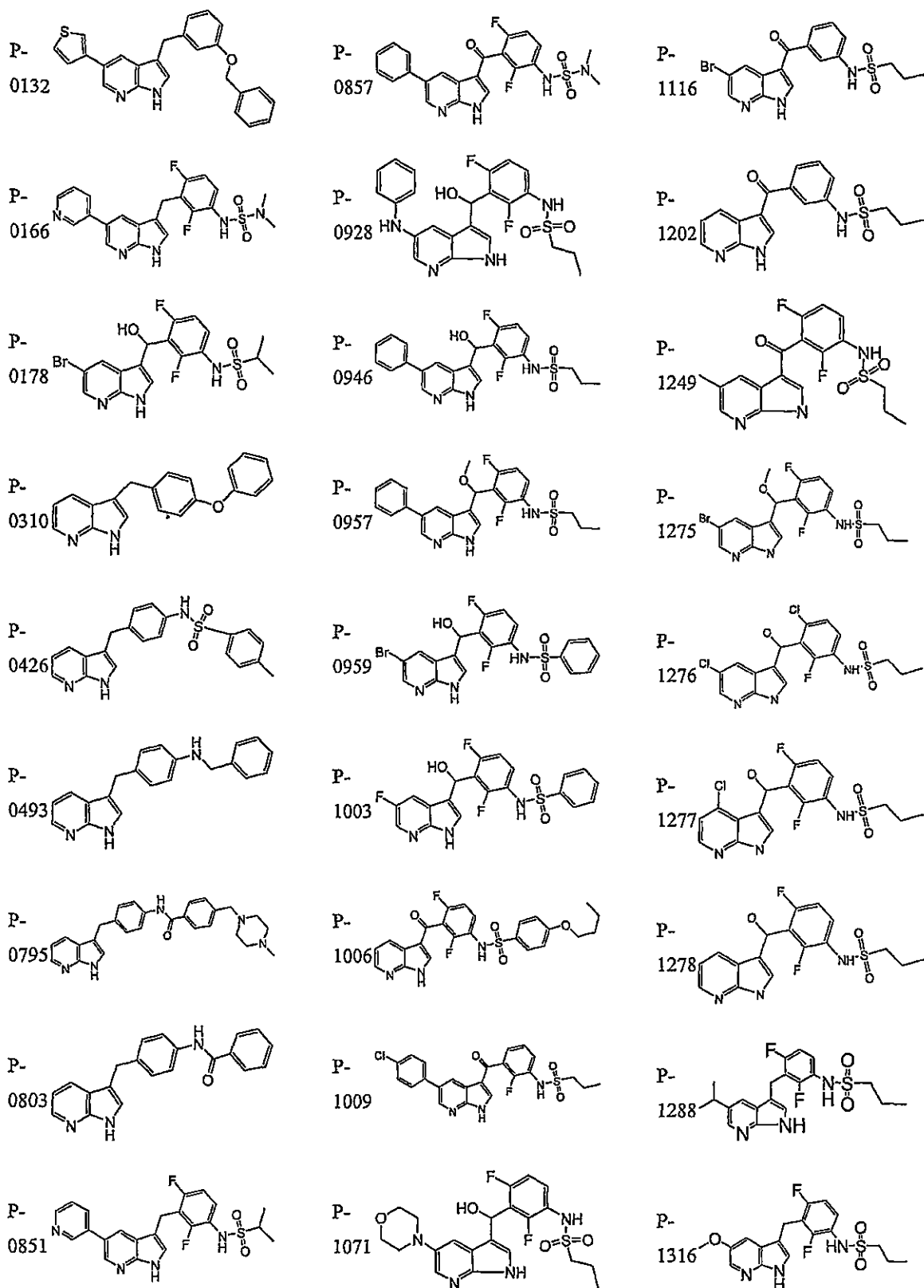
Step 5 – Preparation of 5-Fluoro-2-methoxy-4-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl-phenol (649):

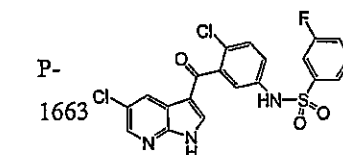
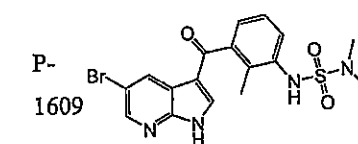
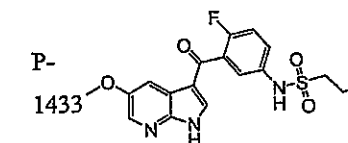
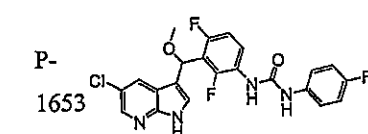
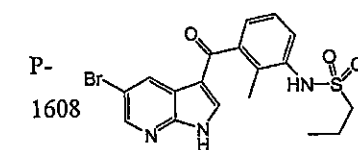
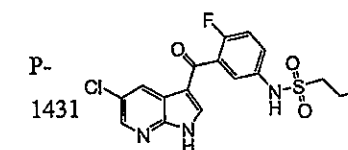
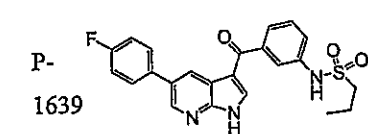
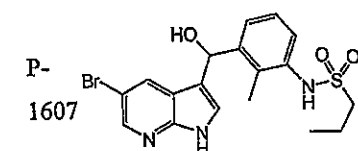
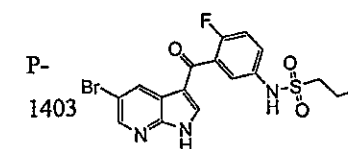
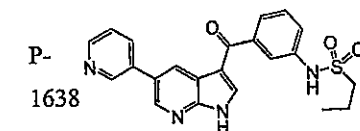
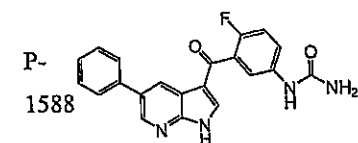
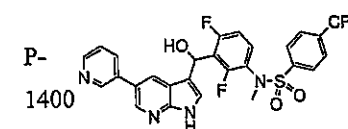
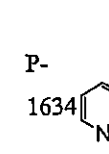
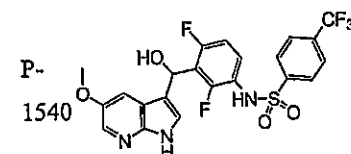
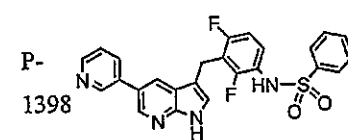
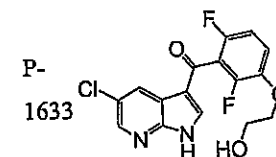
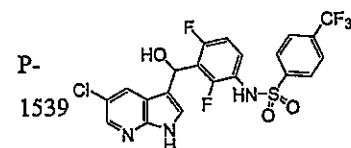
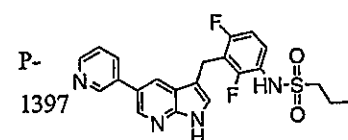
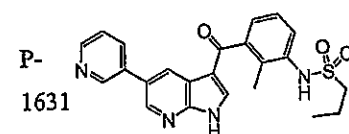
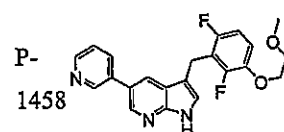
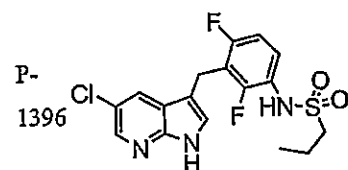
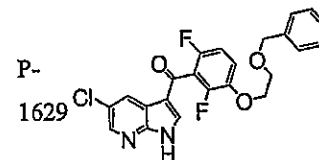
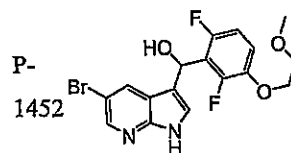
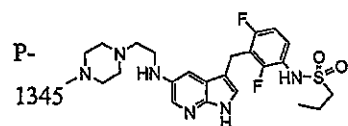
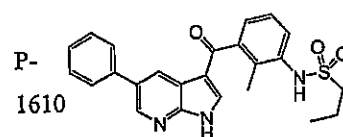
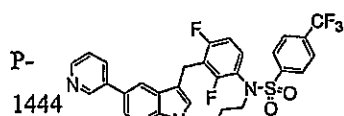
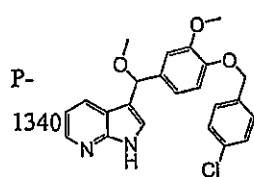
[0502] 3-(4-Benzyloxy-2-fluoro-5-methoxy-benzyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (**657**, 0.831 g, 1.60 mmol) was dissolved in methanol (40 mL) and tetrahydrofuran (40 mL). 10% Palladium on carbon (3.41 g) was added. The reaction was shaken at 50 psi for 1 hour. The reaction was filtered through Celite and washed with methanol. The organic portion was passed through celite several times until a clear solution was obtained. The organic portion was concentrated under reduced pressure to provide the desired compound as an off-white solid (**649**, 587 mg, 86%). MS (ESI) $[M+H]^+ = 429.5$.

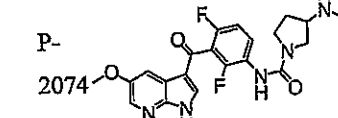
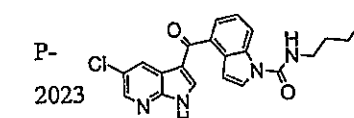
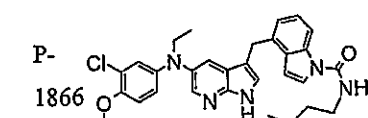
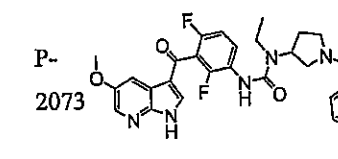
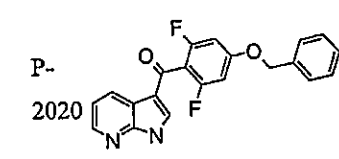
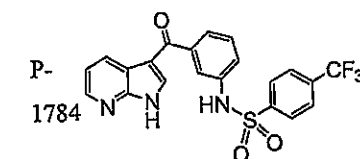
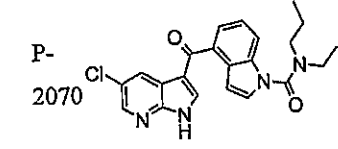
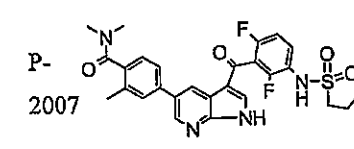
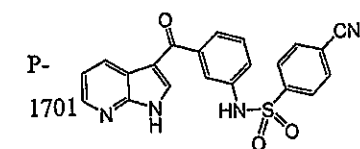
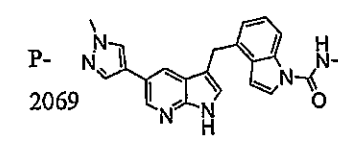
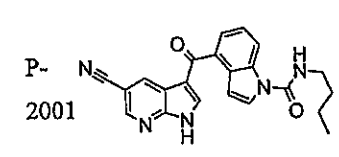
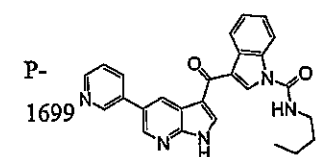
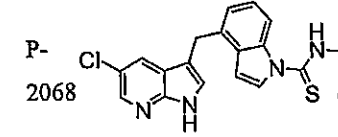
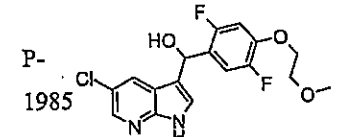
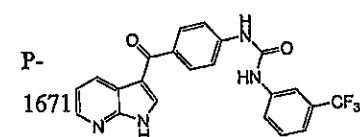
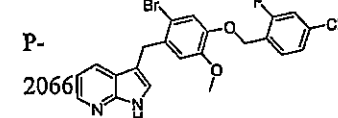
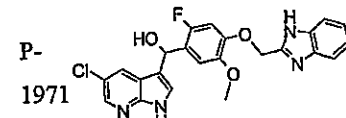
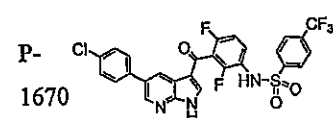
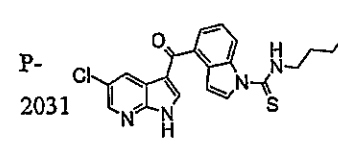
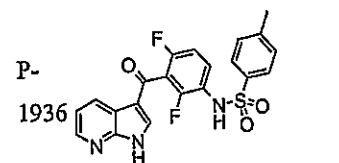
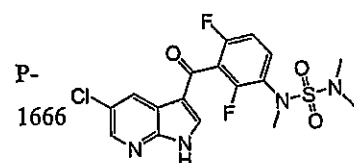
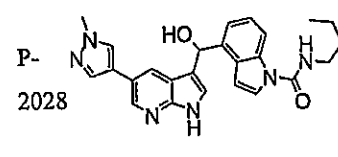
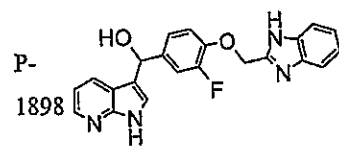
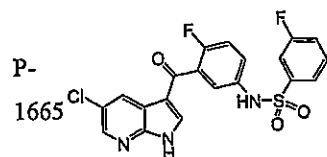
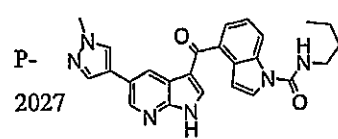
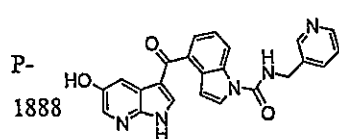
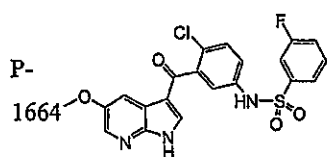
Example 58: Additional compounds

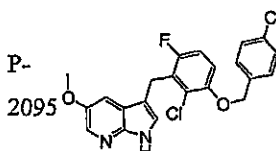
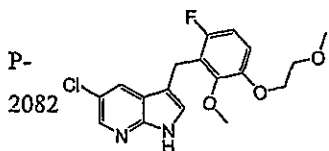
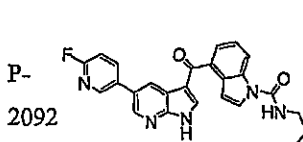
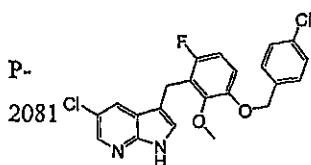
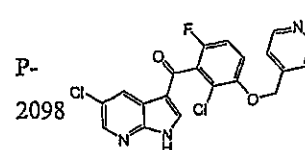
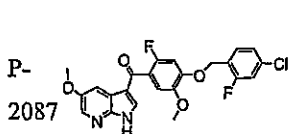
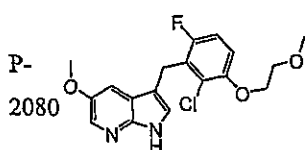
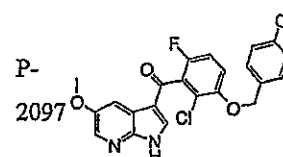
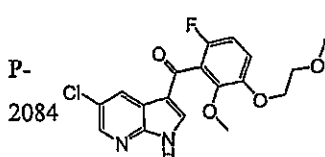
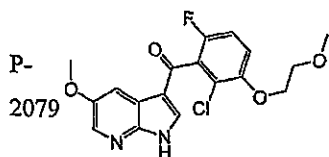
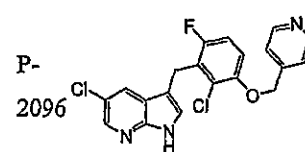
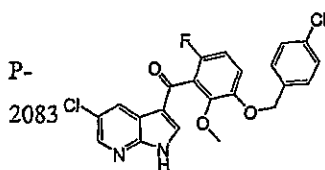
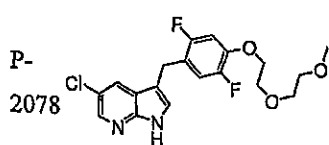
[0503] Additional compounds of the invention were synthesized following the methods of the Examples above, or similar methods known to those of skill in the art, and are shown in the following Table 1.

Table 1. Additional compounds of the invention.









Example 59: Kinase Activity Assays

[0504] AlphaScreen assay was used to screen kinases. The assay is dependent on the phosphorylation of a peptide substrate. In this assay, an antibody that recognizes phosphorylated substrate is bound to an acceptor bead. The peptide substrate is attached to biotin, which binds to a donor bead that contains streptavidin. Thus phosphorylated substrate is bound by antibody and streptavidin, bringing the donor and acceptor beads into close proximity when kinase is not inhibited. The donor produces singlet oxygen which results in emission from the acceptor when they are in close proximity. Conversely, when kinase is inhibited, the donor and acceptor beads are not associated and the emission from the acceptor is reduced. The fluorescence signal vs. compound concentration was used to determine the IC_{50} values.

Genetic Engineering

[0505] For B-Raf V600E and Kit, preparation of the kinase was required. Plasmids encoding a selection of kinase enzymes were engineered using common polymerase chain reaction (PCR)

methods. The relevant DNA sequences and encoded protein sequences used in the assay are shown for each (see below). Complementary DNA cloned from various human tissues were purchased from Invitrogen, and these were used as substrates in the PCR reactions. Specific custom synthetic oligonucleotide primers (Invitrogen see below) were designed to initiate the PCR product, and also to provide the appropriate restriction enzyme cleavage sites for ligation with the plasmids. Additional pairs of oligonucleotides (see below) were used to introduce mutations into the coding sequence to alter the sequence for enzyme activation in BRAF. In the case of KIT, the entire sequence encoding the enzyme was made through a gene synthesis procedure, using custom synthetic oligonucleotides covering the entire coding sequence (Invitrogen).

[0506] The plasmids used for ligation with the kinase-encoding inserts were derivatives of either pET (Novagen) for expression using *E. coli*, or pFastBac (Invitrogen) for expression using baculovirus infection of insect cell cultures. In each of these cases the kinase was engineered to include a Histidine tag for purification using metal affinity chromatography.

[0507] The kinase-encoding plasmids were engineered as bicistronic mRNA to co-express a second protein that modifies the kinase protein during its expression in the host cell. For Kit, protein tyrosine phosphatase 1B (PTP), was co-expressed for dephosphorylation of the phosphotyrosines. For BRAF, the chaperone CDC37, was co-expressed for more efficient protein folding of the BRAF.

[0508] Plasmid encoding phosphorylation substrate protein MEK1, a substrate for BRAF, was expressed as N-terminal GST fusion and C-terminal biotinylation fusion, using pGEX vectors (Amersham) modified to include sequences encoding a C-terminal biotinylation tag.

Protein Expression in *E. coli* and Purification.

[0509] For protein expression, plasmid containing KIT was transformed into *E. coli* strain BL21 (DE3) Codonplus RILP (Invitrogen) and transformants selected for growth on LB agar plates containing appropriate antibiotics. Single colonies were grown overnight at 37°C in 200 ml TB (Terrific broth) media. 16x1L of fresh TB media in 2.8L flasks were inoculated with 10 mL of overnight culture and grown with constant shaking at 37°C. Once cultures reached an absorbance of 1.0 at 600 nm, IPTG was added and cultures were allowed to grow for a further 12 to 18 hrs at temperatures ranging from 12-30°C. Cells were harvested by centrifugation and pellets frozen at -80°C until ready for lysis.

[0510] For protein Purification; frozen *E. coli* cell pellets were resuspended in lysis buffer and lysed using standard mechanical methods. Soluble proteins were purified via poly-Histidine tags using immobilized metal affinity purification IMAC. The kinases have been purified using a 3 step purification process utilizing; IMAC, size exclusion chromatography and ion exchange

chromatography. The poly-Histidine tag was removed as needed using Thrombin (Calbiochem). For B-Raf, the purification protocol required 5mM MgCl₂ throughout purification in order to stabilize soluble protein during purification and concentration.

Baculovirus Expression Vector System, Virus production:

[0511] The transfection of a monolayer of *Spodoptera frugiperda* (Sf9) cells was performed utilizing a bacmid containing the BRAF and Cellfectin (Invitrogen) transfection reagent in antibiotic-free, serum-free Grace's complete media (Invitrogen). After a five hour incubation, the transfection media was removed, and the monolayer was fed with Grace's media containing 10% FBS and antibiotics. After a 72 to 96 hr incubation, the cell supernatant containing the virus was harvested. The titer of the virus stock was then determined using a baculovirus titer kit (BD). The virus stock was then expanded using low Multiplicity of Infection (MOI of 0.1) cultures and harvested 48 hrs post-infection. The titer of the expanded virus stock was then determined for use in recombinant protein production.

Protein Production:

[0512] The protein expression level was optimized by varying the MOI (1-10) and time of harvest (48-72 hrs). Sf9 cells were adapted to SF-900 II serum-free media and grown in suspension in spinner flasks. The cell suspension was then used to inoculate a Wave bioreactor for 25L production scale. Cells were harvested 48-72 hrs post-infection and stored at -80°C until ready for lysis. Proteins were purified similarly to those expressed in *E. coli*.

Kinase assay

[0513] AlphaScreen assays were done using compounds dissolved in DMSO to a concentration of 20 mM. The compounds were diluted accordingly to the desired final concentrations in each sample well, using 1:3 serial dilution for a total of 8 concentration points. Plates were prepared such that each kinase reaction is 20 µl in 1x kinase buffer, 5% DMSO and 10 µM ATP. Kit and Fms were alternatively assayed with 100 µM ATP. After incubation of the kinase reaction for 1 hour at room temperature, 5 µl of donor beads in stop buffer was added, the sample was mixed and incubated for 20 minutes at room temperature before adding 5 µl of acceptor beads in stop buffer. The samples were incubated for 60 minutes at room temperature and the signal per well was read on AlphaQuest reader. Phosphorylated substrate results in binding of the antibody and association of the donor and acceptor beads such that signal correlates with kinase activity. The signal vs. compound concentration was used to determine the IC₅₀. The conditions used for 20 µl reaction for each kinase are described as follows.

[0514] For Raf kinases, B-Raf and c-Raf-1 were purchased from Upstate Biotechnology and B-Raf V600E was prepared using plasmid P4254 expressed in Sf9 cells as described above. For each, the final assay conditions were 0.1 ng kinase, 100 nM biotin-MEK1 substrate (prepared as described above) in 1x kinase buffer (50 mM HEPES pH 7.0, 50 mM NaCl, 2 mM MgCl₂, 1 mM MnCl₂, 1 mM DTT, 0.01% Tween-20), followed by Streptavidin coated donor bead (10 µg/ml, Perkin Elmer Life Science) and Protein A coated, bound to anti phosphor MEK1/2 antibody acceptor bead (10 µg/ml, CellSignal) in stop buffer (50 mM EDTA in 1x kinase buffer).

[0515] For Jnk kinases, Jnk1 and Jnk3 were purchased from Upstate Biotechnology and Jnk2 from Roche Protein Expression Group (Indianapolis, IN). The final assay conditions were 0.1 ng kinase (Jnk1 and Jnk3) or 0.05 ng kinase (Jnk2), 30 nM biotin-ATF2 (Upstate Biotechnology) in 1x kinase buffer (20 mM HEPES pH 7.0, 10 mM MgCl₂, 1 mM DTT, 0.01% Tween-20), followed by Streptavidin coated donor bead (10 µg/ml, Perkin Elmer Life Science) and Protein A coated, bound to anti phosphor ATF2 antibody acceptor bead (10 µg/ml, CellSignal) in stop buffer (50 mM EDTA in 1x kinase buffer).

[0516] Fms was purchased from Upstate Biotechnology. The final assay conditions were 0.5 ng kinase, 30 nM biotin-(E4Y)₁₀ (Upstate Biotechnology) in 1x kinase buffer (8 mM MOPS pH 7.4, 2 mM MgCl₂, 8 mM MnCl₂, 2 mM DTT, 0.01% Tween-20), followed by Streptavidin coated donor bead (20 µg/ml, Perkin Elmer Life Science) and PY20 antibody coated acceptor bead (20 µg/ml, Perkin Elmer Life Science) in stop buffer (8 mM MOPS, pH 7.4, 100 mM EDTA, 0.3% BSA). For assays at 100 µM ATP, the 1x buffer was 8 mM MOPS pH 7.0, 2 mM MgCl₂, 8 mM MnCl₂, 2 mM DTT, 50 mM NaCl, 0.01% BSA and 0.01% Tween-20 and stop buffer was 8 mM MOPS, pH 7.0, 100 mM EDTA, 0.01% BSA.

[0517] Kit was either purchased from Cell Signaling Technology or prepared using plasmid P1332 expressed in *E. coli* as described above. The final assay conditions were 0.1 ng kinase, 100 nM biotin-(E4Y)₃ (Open Source Biotech, Inc.) in 1x kinase buffer (50mM HEPES pH7.2, 5mM MgCl₂, 5mM MnCl₂, 0.2% BSA, 0.01% NP-40), followed by Streptavidin coated donor bead (1 µg/ml, Perkin Elmer Life Science) and PY20 antibody coated acceptor bead (1 µg/ml, Perkin Elmer Life Science) in stop buffer (50 mM EDTA in 1x kinase buffer). For assays at 100 µM ATP, 1 ng kinase was used and the 1x buffer was 8 mM MOPS pH 7.0, 1 mM MgCl₂, 2 mM MnCl₂, 1 mM DTT, 0.001% BSA and 0.01% Tween-20, with substrate of 30 nM biotin-(E4Y)₁₀ (Upstate Biotechnology). Beads were at 10 µg/ml in stop buffer of 8 mM MOPS, pH 7.0, 100 mM EDTA, 0.3% BSA.

[0518] Compounds screened having IC₅₀ of less than 10 µM are shown in tables 2a (B-Raf), 2b (B-Raf V600E), 2c (c-Raf-1), 2d (Fms), 2e (Jnk1), 2f (Jnk2), 2g (Jnk3), and 2h (Kit) as follows.

Table 2a. Compounds with activity toward kinase B-Raf with IC₅₀ ≤ 10 µM.

B-Raf	P-0007, P-0088, P-0166, P-0178, P-0188, P-0310, P-0356, P-0636, P-0685, P-0728, P-0753, P-0773, P-0774, P-0776, P-0798, P-0805, P-0806, P-0818, P-0837, P-0848, P-0850, P-0851, P-0853, P-0857, P-0860, P-0867, P-0874, P-0876, P-0877, P-0885, P-0889, P-0896, P-0897, P-0898, P-0902, P-0904, P-0907, P-0910, P-0911, P-0912, P-0913, P-0928, P-0931, P-0933, P-0937, P-0944, P-0946, P-0947, P-0952, P-0954, P-0955, P-0956, P-0958, P-0959, P-0983, P-0984, P-0991, P-0997, P-1003, P-1004, P-1006, P-1009, P-1013, P-1020, P-1028, P-1056, P-1116, P-1243, P-1244, P-1246, P-1247, P-1249, P-1250, P-1251, P-1252, P-1253, P-1254, P-1255, P-1256, P-1257, P-1258, P-1259, P-1260, P-1261, P-1262, P-1263, P-1264, P-1265, P-1266, P-1267, P-1268, P-1269, P-1270, P-1288, P-1289, P-1317, P-1318, P-1397, P-1431, P-1432, P-1433, P-1445, P-1446, P-1447, P-1455, P-1467, P-1486, P-1532, P-1534, P-1539, P-1541, P-1542, P-1544, P-1546, P-1547, P-1548, P-1549, P-1552, P-1553, P-1554, P-1559, P-1566, P-1567, P-1568, P-1569, P-1570, P-1576, P-1580, P-1581, P-1582, P-1583, P-1586, P-1589, P-1590, P-1591, P-1596, P-1597, P-1598, P-1599, P-1600, P-1602, P-1608, P-1609, P-1610, P-1612, P-1613, P-1616, P-1621, P-1627, P-1630, P-1631, P-1636, P-1637, P-1638, P-1639, P-1656, P-1660, P-1663, P-1664, P-1665, P-1670, P-1671, P-1687, P-1700, P-1701, P-1702, P-1703, P-1704, P-1705, P-1706, P-1707, P-1708, P-1709, P-1710, P-1711, P-1712, P-1713, P-1714, P-1715, P-1716, P-1717, P-1718, P-1719, P-1720, P-1721, P-1722, P-1723, P-1724, P-1725, P-1726, P-1727, P-1728, P-1729, P-1730, P-1731, P-1732, P-1733, P-1734, P-1735, P-1736, P-1737, P-1738, P-1739, P-1740, P-1741, P-1742, P-1746, P-1747, P-1748, P-1749, P-1750, P-1751, P-1752, P-1753, P-1755, P-1756, P-1757, P-1758, P-1759, P-1760, P-1762, P-1763, P-1764, P-1765, P-1766, P-1767, P-1768, P-1769, P-1770, P-1771, P-1772, P-1773, P-1774, P-1775, P-1776, P-1777, P-1778, P-1779, P-1780, P-1781, P-1782, P-1783, P-1784, P-1798, P-1799, P-1800, P-1802, P-1804, P-1816, P-1817, P-1818, P-1819, P-1822, P-1823, P-1825, P-1827, P-1828, P-1839, P-1840, P-1841, P-1842, P-1864, P-1865, P-1871, P-1872, P-1873, P-1878, P-1879, P-1881, P-1882, P-1907, P-1912, P-1916, P-1980, P-1996, P-1997, P-1998, P-2005, P-2006, P-2007, P-2012, P-2013
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Table 2b. Compounds with activity toward kinase B-Raf V600E with $IC_{50} \leq 10 \mu M$.

B-Raf V600E	P-0007, P-0088, P-0166, P-0178, P-0188, P-0356, P-0493, P-0636, P-0685, P-0728, P-0753, P-0773, P-0774, P-0776, P-0798, P-0803, P-0805, P-0806, P-0818, P-0837, P-0848, P-0850, P-0851, P-0853, P-0857, P-0860, P-0867, P-0874, P-0876, P-0877, P-0885, P-0889, P-0896, P-0897, P-0898, P-0902, P-0904, P-0907, P-0910, P-0911, P-0912, P-0913, P-0928, P-0931, P-0933, P-0937, P-0944, P-0946, P-0947, P-0950, P-0952, P-0954, P-0955, P-0956, P-0957, P-0958, P-0959, P-0964, P-0971, P-0983, P-0984, P-0991, P-0997, P-1003, P-1004, P-1006, P-1009, P-1013, P-1015, P-1020, P-1028, P-1056, P-1071, P-1090, P-1116, P-1131, P-1243, P-1244, P-1246, P-1247, P-1249, P-1250, P-1251, P-1252, P-1253, P-1254, P-1255, P-1256, P-1257, P-1258, P-1259, P-1260, P-1261, P-1262, P-1263, P-1264, P-1265, P-1266, P-1267, P-1269, P-1270, P-1288, P-1289, P-1316, P-1317, P-1318, P-1345, P-1396, P-1397, P-1398, P-1403, P-1431, P-1432, P-1433, P-1444, P-1445, P-1446, P-1447, P-1449, P-1450, P-1455, P-1462, P-1466, P-1467, P-1470, P-1471, P-1486, P-1495, P-1531, P-1532, P-1534, P-1539, P-1540, P-1541, P-1542, P-1544, P-1545, P-1546, P-1547, P-1548, P-1549, P-1552, P-1553, P-1554, P-1559, P-1566, P-1567, P-1568, P-1569, P-1570, P-1572, P-1575, P-1576, P-1581, P-1582, P-1583, P-1586, P-1589, P-1590, P-1591, P-1594, P-1596, P-1597, P-1598, P-1599, P-1600, P-1601, P-1602, P-1606, P-1607, P-1608, P-1609, P-1610, P-1611, P-1612, P-1613, P-1621, P-1627, P-1630, P-1631, P-1636, P-1637, P-1638, P-1639, P-1656, P-1660, P-1663, P-1664, P-1665, P-1666, P-1670, P-1671, P-1687, P-1698, P-1700, P-1701, P-1702, P-1703, P-1704, P-1705, P-1706, P-1707, P-1708, P-1709, P-1710, P-1711, P-1712, P-1713, P-1714, P-1715, P-1716, P-1717, P-1718, P-1719, P-1720, P-1721, P-1722, P-1723, P-1724, P-1725,
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	P-1726, P-1727, P-1728, P-1729, P-1730, P-1731, P-1732, P-1733, P-1734, P-1735, P-1736, P-1737, P-1738, P-1739, P-1740, P-1741, P-1742, P-1746, P-1747, P-1748, P-1749, P-1750, P-1751, P-1752, P-1753, P-1755, P-1756, P-1757, P-1758, P-1759, P-1760, P-1762, P-1763, P-1764, P-1765, P-1766, P-1767, P-1768, P-1769, P-1770, P-1771, P-1772, P-1773, P-1774, P-1775, P-1776, P-1777, P-1778, P-1779, P-1780, P-1781, P-1782, P-1783, P-1784, P-1797, P-1798, P-1799, P-1800, P-1802, P-1804, P-1816, P-1817, P-1818, P-1819, P-1822, P-1823, P-1828, P-1839, P-1840, P-1841, P-1842, P-1843, P-1864, P-1865, P-1871, P-1872, P-1873, P-1878, P-1879, P-1881, P-1882, P-1907, P-1912, P-1916, P-1980, P-1996, P-1997, P-1998, P-2005, P-2006, P-2007, P-2012, P-2013
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Table 2c. Compounds with activity toward kinase c-Raf-1 with $IC_{50} \leq 10 \mu M$

c-Raf-1:	P-0007, P-0088, P-0166, P-0178, P-0188, P-0356, P-0636, P-0685, P-0728, P-0753, P-0773, P-0774, P-0776, P-0798, P-0805, P-0806, P-0818, P-0837, P-0848, P-0850, P-0851, P-0853, P-0857, P-0860, P-0867, P-0874, P-0876, P-0877, P-0885, P-0889, P-0896, P-0897, P-0898, P-0902, P-0904, P-0907, P-0910, P-0911, P-0912, P-0913, P-0928, P-0931, P-0933, P-0937, P-0944, P-0947, P-0950, P-0952, P-0954, P-0955, P-0956, P-0957, P-0958, P-0959, P-0964, P-0971, P-0983, P-0991, P-0997, P-1003, P-1004, P-1006, P-1009, P-1013, P-1015, P-1020, P-1028, P-1056, P-1071, P-1243, P-1244, P-1246, P-1247, P-1249, P-1250, P-1251, P-1253, P-1254, P-1255, P-1256, P-1257, P-1258, P-1260, P-1261, P-1262, P-1265, P-1288, P-1289, P-1316, P-1317, P-1318, P-1396, P-1397, P-1398, P-1403, P-1431, P-1432, P-1433, P-1455, P-1541, P-1542, P-1546, P-1547, P-1581, P-1583, P-1630, P-1671, P-1712, P-1713, P-1714, P-1733, P-1737, P-1738, P-1739, P-1740, P-1783, P-1839, P-1864, P-1871, P-1873, P-1878, P-1879, P-1881, P-1882
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Table 2d. Compounds with activity toward kinase Fms with $IC_{50} \leq 10 \mu M$

Fms:	P-0007, P-0088, P-0166, P-0636, P-0685, P-0753, P-0773, P-0774, P-0798, P-0805, P-0806, P-0818, P-0837, P-0848, P-0850, P-0851, P-0853, P-0857, P-0867, P-0874, P-0876, P-0885, P-0898, P-0911, P-0913, P-0931, P-0933, P-0952, P-0954, P-0955, P-0956, P-0958, P-1009, P-1013, P-1246, P-1247, P-1249, P-1250, P-1251, P-1252, P-1253, P-1255, P-1259, P-1260, P-1262, P-1263, P-1264, P-1265, P-1266, P-1267, P-1269, P-1289, P-1316, P-1317, P-1318, P-1340, P-1397, P-1400, P-1403, P-1431, P-1432, P-1433, P-1445, P-1447, P-1449, P-1450, P-1455, P-1462, P-1466, P-1467, P-1470, P-1471, P-1486, P-1495, P-1496, P-1532, P-1534, P-1541, P-1542, P-1544, P-1545, P-1546, P-1547, P-1548, P-1549, P-1552, P-1553, P-1554, P-1559, P-1566, P-1567, P-1568, P-1569, P-1570, P-1571, P-1572, P-1575, P-1576, P-1580, P-1581, P-1583, P-1586, P-1587, P-1589, P-1591, P-1594, P-1595, P-1596, P-1597, P-1598, P-1599, P-1602, P-1606, P-1608, P-1609, P-1610, P-1611, P-1612, P-1613, P-1615, P-1616, P-1618, P-1621, P-1625, P-1627, P-1630, P-1631, P-1636, P-1637, P-1638, P-1639, P-1652, P-1653, P-1654, P-1656, P-1657, P-1660, P-1663, P-1664, P-1665, P-1670, P-1671, P-1687, P-1700, P-1701, P-1702, P-1703, P-1704, P-1705, P-1706, P-1707, P-1708, P-1709, P-1710, P-1711, P-1712, P-1713, P-1714, P-1715, P-1716, P-1717, P-1718, P-1719, P-1720, P-1721, P-1722, P-1723, P-1724, P-1725, P-1726, P-1727, P-1728, P-1729, P-1730, P-1731, P-1732, P-1733, P-1734, P-1735, P-1736, P-1737, P-1738, P-1739, P-1740, P-1741, P-1742, P-1746, P-1747, P-1748, P-1749, P-1750, P-1751, P-1753, P-1754, P-1755, P-1756, P-1757, P-1758, P-1759, P-1760, P-1761, P-1762, P-1763, P-1764, P-1765, P-1766, P-1767, P-1768, P-1769, P-1771, P-1772, P-1773, P-1774, P-1775, P-1776, P-1778, P-1779, P-1780, P-1781, P-1782, P-1783, P-1784, P-1796, P-1798, P-1799, P-1800, P-1802, P-1803, P-1804, P-1816, P-1817, P-1818, P-1819, P-1821, P-1822, P-1827, P-1828, P-1839, P-1840, P-1864, P-1871, P-1872, P-1873, P-1878, P-1879, P-1881, P-1882, P-1907, P-1912, P-1916,
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P-1980, P-1996, P-1997, P-1998, P-2005, P-2006, P-2007, P-2012, P-2013
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Table 2e. Compounds with activity toward kinase Jnk1 with $IC_{50} \leq 10 \mu M$

Jnk1:	P-0088, P-0636, P-0685, P-0728, P-0753, P-0774, P-0848, P-0850, P-0851, P-0853, P-0860, P-0876, P-0897, P-0956, P-0958, P-0991, P-0997, P-1009, P-1251, P-1253, P-1256, P-1260, P-1262, P-1266, P-1288, P-1289, P-1317, P-1318, P-1400, P-1432, P-1433, P-1445, P-1446, P-1447, P-1486, P-1534, P-1546, P-1547, P-1548, P-1549, P-1553, P-1554, P-1566, P-1567, P-1570, P-1576, P-1589, P-1591, P-1596, P-1602, P-1610, P-1611, P-1618, P-1621, P-1627, P-1631, P-1636, P-1637, P-1638, P-1639, P-1656, P-1660, P-1687, P-1702, P-1706, P-1707, P-1708, P-1720, P-1722, P-1723, P-1724, P-1725, P-1727, P-1730, P-1731, P-1742, P-1748, P-1749, P-1750, P-1751, P-1755, P-1756, P-1757, P-1759, P-1760, P-1764, P-1765, P-1767, P-1770, P-1775, P-1776, P-1777, P-1778, P-1779, P-1827, P-1828, P-1839, P-1842, P-1864, P-1873, P-1878, P-1879, P-1896, P-1897, P-1898, P-2007
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Table 2f. Compounds with activity toward kinase Jnk2 with $IC_{50} \leq 10 \mu M$

Jnk2:	P-0088, P-0685, P-1253, P-1318, P-1445, P-1447, P-1486, P-1547, P-1548, P-1554, P-1566, P-1567, P-1570, P-1575, P-1576, P-1589, P-1591, P-1602, P-1611, P-1621, P-1627, P-1656, P-1671, P-1687, P-1700, P-1702, P-1711, P-1720, P-1722, P-1723, P-1724, P-1727, P-1728, P-1729, P-1730, P-1731, P-1732, P-1737, P-1742, P-1748, P-1749, P-1750, P-1751, P-1753, P-1755, P-1756, P-1757, P-1759, P-1760, P-1764, P-1765, P-1767, P-1770, P-1776, P-1777, P-1778, P-1779, P-1827, P-1828, P-1864, P-2007
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Table 2g. Compounds with activity toward kinase Jnk3 with $IC_{50} \leq 10 \mu M$

Jnk3:	P-0088, P-0132, P-0166, P-0636, P-0753, P-0774, P-0851, P-0991, P-1253, P-1289, P-1317, P-1318, P-1400, P-1445, P-1447, P-1486, P-1534, P-1546, P-1547, P-1548, P-1554, P-1566, P-1567, P-1570, P-1576, P-1589, P-1591, P-1610, P-1611, P-1618, P-1621, P-1636, P-1687, P-1702, P-1703, P-1704, P-1706, P-1707, P-1713, P-1716, P-1720, P-1722, P-1724, P-1742, P-1748, P-1749, P-1750, P-1753, P-1756, P-1757, P-1759, P-1764, P-1765, P-1767, P-1770, P-1775, P-1776, P-1777, P-1827, P-1828, P-1864, P-2007
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Table 2h. Compounds with activity toward kinase Kit with $IC_{50} \leq 10 \mu M$

Kit:	P-0007, P-0088, P-0132, P-0166, P-0636, P-0685, P-0753, P-0773, P-0774, P-0776, P-0798, P-0806, P-0818, P-0837, P-0848, P-0850, P-0851, P-0853, P-0857, P-0860, P-0867, P-0874, P-0876, P-0877, P-0885, P-0889, P-0898, P-0907, P-0910, P-0911, P-0913, P-0931, P-0933, P-0937, P-0952, P-0954, P-0955, P-0956, P-0958, P-0964, P-0983, P-1009, P-1013, P-1246, P-1247, P-1249, P-1250, P-1251, P-1252, P-1253, P-1254, P-1255, P-1256, P-1257, P-1259, P-1260, P-1261, P-1262, P-1263, P-1264, P-1266, P-1267, P-1268, P-1269, P-1275, P-1289, P-1316, P-1317, P-1318, P-1396, P-1397, P-1400, P-1403, P-1431, P-1432, P-1433, P-1445, P-1446, P-1447, P-1449, P-1450, P-1455, P-1462, P-1466, P-1467, P-1470, P-1471, P-1486, P-1495, P-1531, P-1532, P-1534, P-1541, P-1542, P-1544, P-1545, P-1546, P-1547, P-1548, P-1549, P-1552, P-1553, P-1554, P-1559, P-1566, P-1567, P-1568, P-1569, P-1575, P-1576, P-1580, P-1581, P-1582, P-1583, P-1590, P-1591, P-1598, P-1599, P-1630, P-1671, P-1700, P-1703, P-1704, P-1705, P-1706, P-1707, P-1708, P-1709, P-1711, P-1712, P-1713, P-1714, P-1718, P-1719, P-1720, P-1733, P-1737, P-1739, P-1740, P-1767, P-1776, P-1783, P-1798, P-1822, P-1839, P-1840, P-1864, P-1865, P-1871, P-1872, P-1873, P-1878, P-1879, P-1881, P-1882, P-1980, P-1996, P-1997, P-1998
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Plasmid sequence and PCR primer information:**[0519] B-Raf V600E****PCR primers**

BRAF	BRAF437D-S	ACGGGACCATATGGATGATTGGGAGATTCCTGA (SEQ ID NO:___)	4783
	BRAF722K-A	CACTGGTCGACTATTTTGGCAATGAGCGGGCCA (SEQ ID NO:___)	4784
	BRAFV599E-S	GGCTAGCTACAGAAAAATCTCGATGGAG (SEQ ID NO:___)	893
	BRAFV599E-A	CTCCATCGAGATTTTCTGTAGCTAGACC (SEQ ID NO:___)	894

P4254. pFastBacBD-CDC37 BRAF D437-K722-X, V600E

tattccggattattcataccgtcccaccatcgggcgcggatctcggtccgaaacc
 atgtcgtactaccatcaccatcaccatcacgattacgatatcccaacgaccgaaaacctg
 M S Y Y H H H H H D Y D I P T T E N L
 tattttcagggccatatggatgattgggagattcctgatgggcagattacagtgggacaa
 Y F Q G H M D D W E I P D G Q I T V G Q
 agaattggatctggatcatttggaaacagtctacaagggaaagtggcatggtgatgtggca
 R I G S G S F G T V Y K G K W H G D V A
 gtgaaaatggtgaatgtgacagcacctacacctcagcagttacaagccttcaaaaatgaa
 V K M L N V T A P T P Q Q L Q A F K N E
 gtaggagtactcaggaaaacacgacatgtgaatatcctactcttcatgggctattccaca
 V G V L R K T R H V N I L L F M G Y S T
 aagccacaactggctattgttaccagtggtgtgagggctccagcttgatcaccatctc
 K P Q L A I V T Q W C E G S S L Y H H L
 catatcattgagaccaaatttgagatgatcaaacttatagatattgcacgacagactgca
 H I I E T K F E M I K L I D I A R Q T A
 cagggcatggattacttacacgccaagtcaatcatccacagagacctcaagagtaataat
 Q G M D Y L H A K S I I H R D L K S N N
 atatttcttcatgaagacctcacagtaaaaataggtgatttttggtctagctacagaaaaa
 I F L H E D L T V K I G D F G L A T E K
 tctcgatggagtggttcccacagtttgaacagttgtctggatccattttgtggatggca
 S R W S G S H Q F E Q L S G S I L W M A
 ccagaagtcacagaatgcaagataaaaatccatacagctttcagtcagatgtatatgca
 P E V I R M Q D K N P Y S F Q S D V Y A
 tttggaattgttctgtatgaattgatgactggacagttaccttattcaaacatcaacaac
 F G I V L Y E L M T G Q L P Y S N I N N
 agggaccagataatttttatgggtgggacgaggatacctgtctccagatctcagtaaggta
 R D Q I I F M V G R G Y L S P D L S K V
 cggagtaactgtccaaaagccatgaagagattaatggcagagtgccctcaaaaagaaaaga
 R S N C P K A M K R L M A E C L K K K R
 gatgagagaccactctttcccaaattctcgccctctattgagctgctggcccgctcattg
 D E R P L F P Q I L A S I E L L A R S L
 ccaaaatagtcgactagagcctgcagtcctcgaggcatgcggtaccaagctt (SEQ ID NO:___)
 P K - (SEQ ID NO:___)

[0520] Kit

PCR primers

KIT	8K1A	ATGTACGAAGTTCAGTGGAAAGTTGTTGAAGAAATCAACGG (SEQ ID NO:___)	1776
	8K1B	GGTCGATGTAAACGTAGTTGTTACCGTTGATTTCTTCAACAACTTT (SEQ ID NO:___)	1777
	8K2A	AACAACCTACGTTTACATCGACCCGACCCAGCTGCCGTACGAC (SEQ ID NO:___)	1779
	8K2B	GTTACGCGGGAACCTCCATTGTTGGTCGTACGGCAGCTGGGTC (SEQ ID NO:___)	1781
	8K3A	AAATGGGAGTTCCCGCGTAACCGTCTGTCTTTCGGTAAACCC (SEQ ID NO:___)	1782
	8K3B	ACCGAACGCACCCGCACCCAGGGTTTTACCGAAAGACAGAC (SEQ ID NO:___)	1783
	8K4A	GGTGCGGGTGCGTTCGGTAAAGTTGTTGAAGCGACCGGTACG (SEQ ID NO:___)	1784
	8K4B	GCCGCGTCAGATTTGATCAGACCGTACGCGGTGCTTCAAC (SEQ ID NO:___)	1785
	8K5A	CTGATCAAATCTGACGCGGCGATGACCGTTGCGGTAAAAATGC (SEQ ID NO:___)	1786
	8K5B	GTCAGGTGCGCAGACGGTTTTAGCATTTTAACCGCAACGGTCA (SEQ ID NO:___)	1787
	8K6A	AAACCGTCTGCGCACCTGACCGAACGTAAGCGCTGATGTCTG (SEQ ID NO:___)	1788
	8K6B	CCAGGTAAGACAGAACTTTTCAGTTCAGACATCAGCGCTTCACGT (SEQ ID NO:___)	1789
	8K7A	CTGAAAGTTCTGTCTTACCTGGGTAACCATGAACATCGTTAA (SEQ ID NO:___)	1791
	8K7B	GGTGCACGCACCCAGCAGGTTAACGATGTTTCATGTGGTTAC (SEQ ID NO:___)	1792
	8K8A	CTGCTGGGTGCGTGACCATCGGTGGTCCGACCTGGTTATCA (SEQ ID NO:___)	1793
	8K8B	GTCACCGTAGCAGCAGTATTCGGTGATAACCAGGGTCGGACCA (SEQ ID NO:___)	1794
	8K9A	GAATACTGCTGCTACGGTGACCTGCTGAACTTCCTGCGTCGTA (SEQ ID NO:___)	1795
	8K9B	AGAGCAGATGAAAGAGTACAGTTTACGACGCAGGAAGTTCAGC (SEQ ID NO:___)	1796
	8K10A	CGTGACTCTTTCATCTGCTCTAAACAGGAAGACCACGCGGAAG (SEQ ID NO:___)	1797
	8K10B	CAGCAGGTTTTTGTACAGCGCCGCTTCCGCGTGGTCTTCCTGT (SEQ ID NO:___)	1798

8K11A	GCGCTGTACAAAACCTGCTGCACTCTAAAGAACTTCTTGCTC (SEQ ID NO:___)	1799
8K11B	CCATGTATTTCGTTGGTAGAGTCAGAGCAAGAAGATTCTTTAGAGT (SEQ ID NO:___)	1811
8K11A	GACTCTACCAACGAATACATGGACATGAAACCGGGTGTCTTA (SEQ ID NO:___)	1812
8K11B	TCCGCTTTGGTCGGAACAACGTAAGAAACACCCGGTTTCATGT (SEQ ID NO:___)	1813
8K12A	GTTGTTCCGACCAAAGCGGACAAACGTCGTTCTGTTCGTATCG (SEQ ID NO:___)	1814
8K12B	TAACGTCACGTTTCGATGTAAGAACCGATACGAACAGAACGACGTTT (SEQ ID NO:___)	1815
8K13A	TCTTACATCGAACGTGACGTTACCCCGCGATCATGGAAGACG (SEQ ID NO:___)	1816
8K13B	CCAGGTCCAGCGCCAGTTTCGTCGTTCTTCATGATCGCCGG (SEQ ID NO:___)	1817
8K14A	GAACTGGCGCTGGACCTGGAAGACCTGCTGTCTTTCTCTTACC (SEQ ID NO:___)	1818
8K14B	GAACGCCATACCTTTTCGCAACCTGGTAAGAGAAAGACAGCAGGT (SEQ ID NO:___)	1819
8K15A	GTTGCGAAAGGTATGGCGTTCCTGGCGTCTAAAACTGCATCCA (SEQ ID NO:___)	1821
8K15B	CGCGCCGCCAGGTCACGGTGGATGCAGTTTTTAGACGCC (SEQ ID NO:___)	1822
8K16A	CGTGACCTGGCGGCGCGTAACATCCTGCTGACCCACGGTCG (SEQ ID NO:___)	1823
8K16B	ACCGAAGTCGCAGATTTTGGTGATACGACCGTGGGTCAGCAGG (SEQ ID NO:___)	1824
8K17A	ACCAAAATCTGCGACTTCGGTCTGGCGGTGACATCAAAAACG (SEQ ID NO:___)	1825
8K17B	GTTACCTTTAACAACGTAGTTAGAGTCGTTTTTGATGTCACGCGCC (SEQ ID NO:___)	1826
8K18A	TCTAACTACGTTGTTAAAGGTAACGCGGTCTGCCGGTTAAATG (SEQ ID NO:___)	1827
8K18B	GAAGATAGATTCCGCGCCATCCATTTAACCGGCAGACGCGC (SEQ ID NO:___)	1829
8K19A	ATGGCGCCGGAATCTATCTTCAACTGCGTTTACACCTTCGAATC (SEQ ID NO:___)	1831
8K19B	GATACCGTAAGACCAAACGTCAGATTCGAAGGTGTAAACGCAG (SEQ ID NO:___)	1832
8K20A	GACGTTTGGTCTTACGGTATCTTCTGTGGGAACGTCTCTCTC (SEQ ID NO:___)	1833
8K20B	CCTGTGGGAACGTCTCTCTCTGGGTTCTTCTCCGTACCCGG (SEQ ID NO:___)	1834

		(SEQ ID NO:___)	
8K21A	GGTTCTTCTCCGTACCCGGGTATGCCGGTTGACTCTAAATTCTAT	(SEQ ID NO:___)	1835
8K21B	CGGAAACCTTCTTTGATCATTTGTAGAATTAGAGTCAACCGGC	(SEQ ID NO:___)	1836
8K22A	AAAATGATCAAAGAAGGTTTCCGTATGCTGTCTCCGGAACACG	(SEQ ID NO:___)	1837
8K22B	ATGTCGTACATTTCCGCCGGCGCGTGTCCGGAGACAGCATA	(SEQ ID NO:___)	1838
8K23A	CCGGCGGAAATGTACGACATCATGAAAACCTGCTGGGACGCG	(SEQ ID NO:___)	1839
8K23B	AAGGTCGGACGTTTTCAGCGGGTCCGCGTCCAGCAGGTTTTTC	(SEQ ID NO:___)	1841
8K24A	CCGCTGAAACGTCCGACCTTCAAACAGATCGTTCAGCTGATCG	(SEQ ID NO:___)	1842
8K24B	TTGGTAGATTTCAGAGATCTGTTTTTCGATCAGCTGAACGATCTGTT	(SEQ ID NO:___)	1843
8K25A	AAACAGATCTCTGAATCTACCAACCACATCTACTCTAACCTGGC	(SEQ ID NO:___)	1844
8K25B	TGACGGTTCGGAGAGCAGTTCGCCAGGTTAGAGTAGATGTGG	(SEQ ID NO:___)	1845
8K26A	AACTGCTCTCCGAACCGTCAGAAACCGTTGTTGACCACTCTG	(SEQ ID NO:___)	1846
8K26B	GTAGAACCAACAGAGTTGATACGAACAGAGTGGTCAACAACCGGT	(SEQ ID NO:___)	1847
8K27A	CGTATCAACTCTGTTGGTTCTACCGCGTCTTCTTCTCAGCCG	(SEQ ID NO:___)	1848
8K27B	AACGTCGTCGTGAACCAGCAGCGGCTGAGAAGAAGACGCG	(SEQ ID NO:___)	1849
8K-F	GTTGTTTCATATGTACGAAGTTCAGTGGAAAG	(SEQ ID NO:___)	1851
8K-R	GTTGTTTGTGCGACTAAACGTCGTCGTGAACCAGCAG	(SEQ ID NO:___)	1852
KIT COD-K948X	GTTCTTGTGCGACTATTTCTGACGGTTCGGAGAGC	(SEQ ID NO:___)	3411

P1332.N6 BI PTP KIT M552-K948-X COD

taatacgactcactataggggaattgtgagcggataacaattccccctctagaaataattt
tgtttaactttaagaaggagatataccatgggtcaccaccatcaccatcatatgtacgaa
M G H H H H H H M Y E
gttcagtggaaagttgttgaagaaatcaacggtaacaactacgtttacatcgacccgacc
V Q W K V V E E I N G N N Y V Y I D P T
cagctgccgtacgaccacaaatgggagttcccgcgtaaccgtctgtctttcggtaaaacc
Q L P Y D H K W E F P R N R L S F G K T
ctgggtgcgggtgcgttcggtaaaagttgttgaagcggaccggtacgggtctgatcaaactc
L G A G A F G K V V E A T A Y G L I K S
gacgcggcgatgacggttgcggttaaaatgctgaaaccgtctgcgcacctgaccgaacgt
D A A M T V A V K M L K P S A H L T E R
gaagcgtgatgtctgaactgaaagttctgtcttacctgggtaaccacatgaacatcgtt
E A L M S E L K V L S Y L G N H M N I V
aacctgctgggtgcgtgcaccatcgggtgggtccgaccctgggttatcaccgaataactgctgc
N L L G A C T I G G P T L V I T E Y C C
tacggtgacctgctgaacttcctgcgtcgtaaacgtgactctttcatctgctctaaacag
Y G D L L N F L R R K R D S F I C S K Q
gaagaccacgcggaagcggcgctgtacaaaaactgctgcactctaaagaatcttcttgc
E D H A E A A L Y K N L L H S K E S S C
tctgactctaccaacgaatacatggacatgaaaccgggtgtttcttacgttggtccgacc
S D S T N E Y M D M K P G V S Y V V P T
aaagcggacaaaacgtcggttctgttcgtatcggttcttacatcgaacgtgacgttaccccg
K A D K R R S V R I G S Y I E R D V T P
gcatcatggaagacgacgaactggcgctggacctggaagacctgctgtctttctcttac
A I M E D D E L A L D L E D L L S F S Y
caggttgcaaaaggtatggcggttcctggcgctctaaaaactgcatccaccgtgacctggcg
Q V A K G M A F L A S K N C I H R D L A
gcgcgtaacatcctgctgacccacggctcgtatcaccaaaatctgcgacttcgggtctggcg
A R N I L L T H G R I T K I C D F G L A
cgtgacatcaaaaacgactctaactacgttggttaaaggtaacgcgcgtctgccggttaaa
R D I K N D S N Y V V K G N A R L P V K
tggatggcgccggaatctatcttcaactgcgtttacaccttcgaatctgacgtttggtct
W M A P E S I F N C V Y T F E S D V W S
tacggtatcttctgtgggaactgttctctctgggttcttctcgtaccggggtatgccg
Y G I F L W E L F S L G S S P Y P G M P
gttgactctaaattctacaaaatgatcaaagaagggttccgtatgctgtctccggaacac
V D S K F Y K M I K E G F R M L S P E H
gcgcggcggaatgtacgacatcatgaaaacctgctgggacgcggaccgctgaaacgt
A P A E M Y D I M K T C W D A D P L K R
ccgaccttcaaacagatcggttcagctgatcgaaaaacagatctctgaatctaccaaccac
P T F K Q I V Q L I E K Q I S E S T N H
atctactctaactggcgaaactgctctccgaaccgtcagaaatagtcgactgaaaaagga
I Y S N L A N C S P N R Q K - (SEQ ID NO: ____)
agagt (SEQ ID NO: ____)

[0521] MEK1 substrate

PCR primers

MEK1	MEK1-S	CGGGTCCCATATGCCCAAGAAGAAGCCGAC (SEQ ID NO: ____)	755
	MEK-HIS	GTTTCGTTGTGCGACGACGCCAGCAGCATGGGTTG (SEQ ID NO: ____)	2127
	K97A-1 (K104A)	CTAATTCATCTGGAGATCGCGCCCGCAATCCGG (SEQ ID NO: ____)	2023
	K97A-2 (K104A)	CCGGATTGCGGGCGCGATCTCCAGATGAATTAG (SEQ ID NO: ____)	2024

P1277.pGEX-BIO MEK1 K97A

atgtcccctatactagggtatttgaaaattaagggccttgtgcaaccactcgacttctt
 M S P I L G Y W K I K G L V Q P T R L L
 ttggaatatcttgaagaaaaatatgaagagcatttgtatgagcgcgatgaaggatataaa
 L E Y L E E K Y E E H L Y E R D E G D K
 tggcgaaacaaaaagtttgaattgggtttggagtttcccaatcttccttattatattgat
 W R N K K F E L G L E F P N L P Y Y I D
 ggtgatgttaaattaacacagtctatggccatcatacgttatatagctgacaagcacaac
 G D V K L T Q S M A I I R Y I A D K H N
 atgttgggtgggtgtccaaaagagcgtgcagagatttcaatgcttgaaggagcggttttg
 M L G G C P K E R A E I S M L E G A V L
 gatattagatacgggtgtttcgagaattgcatatagtaaagactttgaaactctcaaagtt
 D I R Y G V S R I A Y S K D F E T L K V
 gattttcttagcaagctacctgaaatgctgaaaatgttcgaagatcgtttatgtcataaa
 D F L S K L P E M L K M F E D R L C H K
 acatatttaaatggatgatcatgtaaccatcctgacttcatgttgtatgacgctcttgat
 T Y L N G D H V T H P D F M L Y D A L D
 gttgttttatatacattggacccaatgtgcctggatgcgttcccaaaattagtttgttttaa
 V V L Y M D P M C L D A F P K L V C F K
 aaacgtattgaagctatcccacaaattgataagtacttgaaatccagcaagtatatagca
 K R I E A I P Q I D K Y L K S S K Y I A
 tggcctttgcagggctggcaagccacgtttgggtggcgaccatcctccaaaatcggat
 W P L Q G W Q A T F G G G D H P P K S D
 ctggttccgcgtggatctcatatgcccaagaagaagccgacgcccacccagctgaacccg
 L V P R G S H M P K K K P T P I Q L N P
 gcccccgacggctctgcagttaacgggaccagctctgcggagaccaacttgaggcccttg
 A P D G S A V N G T S S A E T N L E A L
 cagaagaagctggaggagctagagcttgatgagcagcagcgaaagcgcttgaggccctt
 Q K K L E E L E L D E Q Q R K R L E A F
 cttaccagaagcagaaggtgggagaactgaaggatgacgactttgagaagatcagtgag
 L T Q K Q K V G E L K D D D F E K I S E
 ctgggggctggcaatggcggtgtggtgttcaagggtctcccaagccttctggcctggtc
 L G A G N G G V V F K V S H K P S G L V
 atggccagagcgttaattcatctggagatcaaaccgcaatccggaaccagatcataagg
 M A R A L I H L E I K P A I R N Q I I R
 gagctgcaggttctgcatgagtgaactctccgtacatcggtgggcttctatgggtgcgttc
 E L Q V L H E C N S P Y I V G F Y G A F
 tacagcagtggcgagatcagtatctgcatggagcacatggatggaggttctctggatcaa
 Y S D G E I S I C M E H M D G G S L D Q
 gtcctgaagaaagctggaagaattcctgaacaaattttaggaaaagtttagcattgctgta
 V L K K A G R I P E Q I L G K V S I A V

ataaaaggcctgacatatctgagggagaagcacaagatcatgcacagagatgtcaagccc
I K G L T Y L R E K H K I M H R D V K P
tccaacatcctagtcactcccgtggggagatcaagctctgtgactttggggtcagcggg
S N I L V N S R G E I K L C D F G V S G
cagctcatcgactccatggccaactccttcgtgggcacaaggtcctacatgtcgccagaa
Q L I D S M A N S F V G T R S Y M S P E
agactccaggggactcattactctgtgcagtcagacatctggagcatgggactgtctctg
R L Q G T H Y S V Q S D I W S M G L S L
gtagagatggcgggttgggaggtatcccatccctcctccagatgccaaggagctggagctg
V E M A V G R Y P I P P P D A K E L E L
atgtttgggtgccaggtggaaggagatgcggctgagacccacccaggccaaggaccccc
M F G C Q V E G D A A E T P P R P R T P
gggaggcccccttagctcatacgggaatggacagccgacctcccatggcaatttttgagttg
G R P L S S Y G M D S R P P M A I F E L
ttggattacatagtcaacgagcctcctccaaaactgcccagtgagggtgttcagtcctggaa
L D Y I V N E P P P K L P S G V F S L E
tttcaagattttgtgaataaatgcttaataaaaaaccccgagagagagcagatttgaag
F Q D F V N K C L I K N P A E R A D L K
caactcatgggttcattgcttttatcaagagatctgatgctgaggaagtggattttgcaggt
Q L M V H A F I K R S D A E E V D F A G
tggctctgctccaccatcggccttaaccagcccagcacaccaacccatgctgctggcgctc
W L C S T I G L N Q P S T P T H A A G V
gtcgacctgaacgacatcttcgaagctcagaaaatcgaatggcacccggttagaattc
V D L N D I F E A Q K I E W H R -

(nucleic acid SEQ ID NO:___)

(polypeptide SEQ ID NO:___)

[0522] Additional examples of certain methods contemplated by the present invention may be found in the following applications: U.S. Prov. App. No. 60/580,898, filed June 17, 2004; U.S. Prov. App. No. 60/682,076, filed May 17, 2005; U.S. Prov. App. No. 60/682,058, filed May 17, 2005; U.S. Prov. App. No. 60/682,063, filed May 17, 2005; U.S. Prov. App. No. 60/682,051, filed May 17, 2005; U.S. Prov. App. No. 60/682,042, filed May 17, 2005; U.S. Prov. App. No. 60/692,750, filed June 22, 2005; and U.S. Prov. App. No. 60/692,960, filed June 22, 2005; each of which are hereby incorporated by reference herein in their entireties including all specifications, figures, and tables, and for all purposes.

[0523] 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.

[0524] 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.

[0525] 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 crystallization or co-crystallization conditions for Ret and Ret surrogate proteins and/or various kinase domain sequences can be used. Thus, such additional embodiments are within the scope of the present invention and the following claims.

[0526] 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. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. 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.

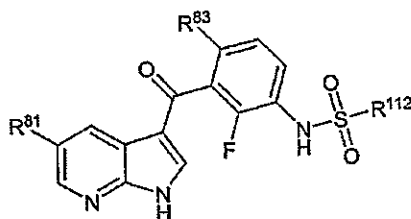
[0527] In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

[0528] 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.

[0529] Thus, additional embodiments are within the scope of the invention and within the following claims.

Claims:

1. A compound having the structure of Formula IIIIm:



Formula IIIIm

or a pharmaceutically acceptable salt thereof,

wherein:

R^{81} is selected from the group consisting of hydrogen, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, - NH_2 , -CN, - NO_2 , -C(O)OH, -S(O) $_2$ NH_2 , -C(O) NH_2 , -C(S) NH_2 , -NHC(O) NH_2 , -NHC(S) NH_2 , -NHS(O) $_2$ NH_2 , -OR ^{68} , -SR ^{68} , -NR ^{69} R ^{68} , -C(O)R ^{68} , -C(S)R ^{68} , -C(O)OR ^{68} , -C(O)NR ^{69} R ^{68} , -C(S)NR ^{69} R ^{68} , -S(O) $_2$ NR ^{69} R ^{68} , -NR ^{69} C(O)R ^{68} , -NR ^{69} C(S)R ^{68} , -NR ^{69} S(O) $_2$ R ^{68} , -NR ^{69} C(O) NH_2 , -NR ^{69} C(O)NR ^{69} R ^{68} , -NR ^{69} C(S) NH_2 , -NR ^{69} C(S)NR ^{69} R ^{68} , -NR ^{69} S(O) $_2$ NH_2 , -NR ^{69} S(O) $_2$ NR ^{69} R ^{68} , -S(O)R ^{68} , and -S(O) $_2$ R ^{68} ;

R^{83} is selected from the group consisting of hydrogen, fluoro and chloro;

R^{112} is selected from the group consisting of optionally substituted C_2 - C_6 alkyl, optionally substituted aryl, optionally substituted heteroaryl, and -NR ^{79} R ^{80} ;

R^{68} is selected from the group consisting of optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, provided, however, that when R^{68} is optionally substituted C_2 - C_6 alkenyl, no alkene carbon thereof is bound to N, S, O, S(O), S(O) $_2$, C(O) or C(S) of -OR ^{68} , -SR ^{68} , -NR ^{69} R ^{68} , -C(O)R ^{68} , -C(S)R ^{68} , -C(O)OR ^{68} , -C(O)NR ^{69} R ^{68} , -C(S)NR ^{69} R ^{68} , -S(O) $_2$ NR ^{69} R ^{68} , -NR ^{69} C(O)R ^{68} , -NR ^{69} C(S)R ^{68} , -NR ^{69} S(O) $_2$ R ^{68} , -NR ^{69} C(O) NH_2 , -NR ^{69} C(O)NR ^{69} R ^{68} , -NR ^{69} C(S) NH_2 , -NR ^{69} C(S)NR ^{69} R ^{68} , -NR ^{69} S(O) $_2$ NH_2 , -NR ^{69} S(O) $_2$ NR ^{69} R ^{68} , -S(O)R ^{68} , or -S(O) $_2$ R ^{68} , optionally substituted C_2 - C_6 alkynyl, provided, however, that when R^{68} is optionally substituted C_2 - C_6 alkynyl, no alkyne carbon thereof is

bound to N, S, O, S(O), S(O)₂, C(O) or C(S) of -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)OR⁶⁸, -C(O)NR⁶⁹R⁶⁸, -C(S)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹C(S)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -NR⁶⁹C(O)NH₂, -NR⁶⁹C(O)NR⁶⁹R⁶⁸, -NR⁶⁹C(S)NH₂, -NR⁶⁹C(S)NR⁶⁹R⁶⁸, -NR⁶⁹S(O)₂NH₂, -NR⁶⁹S(O)₂NR⁶⁹R⁶⁸, -S(O)R⁶⁸, or -S(O)₂R⁶⁸, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R⁶⁹ is selected from the group consisting of hydrogen and optionally substituted C₁-C₆ alkyl; and R⁷⁹ and R⁸⁰ are independently hydrogen or optionally substituted C₁-C₆ alkyl, or R⁷⁹ and R⁸⁰ combine with the nitrogen to which they are attached to form optionally substituted 5-7 membered heterocycloalkyl;

wherein:

optionally substituted C₁-C₆ alkyl as R⁶⁸, R⁶⁹, R⁷⁹, R⁸⁰, or R⁸¹, or C₂₋₆ alkyl as R¹¹², are C₁-C₆ alkyl or C₂₋₆ alkyl, respectively, optionally substituted with one or more substituents selected from the group consisting of -F, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR⁰, -SR⁰, -OC(O)R⁰, -OC(S)R⁰, -C(O)R⁰, -C(S)R⁰, -C(O)OR⁰, -C(S)OR⁰, -S(O)R⁰, -S(O)₂R⁰, -C(O)NHR⁰, -C(S)NHR⁰, -C(O)NR⁰R⁰, -C(S)NR⁰R⁰, -S(O)₂NHR⁰, -S(O)₂NR⁰R⁰, -C(NH)NHR⁰, -C(NH)NR^pR^c, -NHC(O)R⁰, -NHC(S)R⁰, -NR⁰C(O)R⁰, -NR⁰C(S)R⁰, -NHS(O)₂R⁰, -NR⁰S(O)₂R⁰, -NHC(O)NHR⁰, -NHC(S)NHR⁰, -NR⁰C(O)NH₂, -NR⁰C(S)NH₂, -NR⁰C(O)NHR⁰, -NR⁰C(S)NHR⁰, -NHC(O)NR⁰R⁰, -NHC(S)NR⁰R⁰, -NR⁰C(O)NR⁰R⁰, -NR⁰C(S)NR⁰R⁰, -NHS(O)₂NHR⁰, -NR⁰S(O)₂NH₂, -NR⁰S(O)₂NHR⁰, -NHS(O)₂NR⁰R⁰, -NR⁰S(O)₂NR⁰R⁰, -NHR⁰, -NR⁰R⁰, -R^e, -R^f, and -R^g;

optionally substituted C₂-C₆ alkenyl as R⁶⁸ or R⁸¹ is C₂-C₆ alkenyl optionally substituted with one or more substituents selected from the group consisting of -F, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR⁰, -SR⁰, -OC(O)R⁰, -OC(S)R⁰, -C(O)R⁰, -C(S)R⁰, -C(O)OR⁰, -C(S)OR⁰, -S(O)R⁰, -S(O)₂R⁰, -C(O)NHR⁰, -C(S)NHR⁰, -C(O)NR⁰R⁰, -C(S)NR⁰R⁰, -S(O)₂NHR⁰, -S(O)₂NR⁰R⁰, -C(NH)NHR⁰, -C(NH)NR^pR^c, -NHC(O)R⁰, -NHC(S)R⁰, -NR⁰C(O)R⁰, -NR⁰C(S)R⁰, -NHS(O)₂R⁰, -NR⁰S(O)₂R⁰,

-NHC(O)NHR^o, -NHC(S)NHR^o, -NR^oC(O)NH₂, -NR^oC(S)NH₂, -NR^oC(O)NHR^o,
 -NR^oC(S)NHR^o, -NHC(O)NR^oR^o, -NHC(S)NR^oR^o, -NR^oC(O)NR^oR^o,
 -NR^oC(S)NR^oR^o, -NHS(O)₂NHR^o, -NR^oS(O)₂NH₂, -NR^oS(O)₂NHR^o,
 -NHS(O)₂NR^oR^o, -NR^oS(O)₂NR^oR^o, -NHR^o, -NR^oR^o, -R^d, -R^f, and -R^g;

optionally substituted C₂-C₆ alkynyl as R⁶⁸ or R⁸¹ is C₂-C₆ alkynyl
 optionally substituted with one or more substituents selected from the group
 consisting of -F, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂,
 -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂,
 -OR^o, -SR^o, -OC(O)R^o, -OC(S)R^o, -C(O)R^o, -C(S)R^o, -C(O)OR^o, -C(S)OR^o,
 -S(O)R^o, -S(O)₂R^o, -C(O)NHR^o, -C(S)NHR^o, -C(O)NR^oR^o, -C(S)NR^oR^o,
 -S(O)₂NHR^o, -S(O)₂NR^oR^o, -C(NH)NHR^o, -C(NH)NR^oR^o, -NHC(O)R^o,
 -NHC(S)R^o, -NR^oC(O)R^o, -NR^oC(S)R^o, -NHS(O)₂R^o, -NR^oS(O)₂R^o,
 -NHC(O)NHR^o, -NHC(S)NHR^o, -NR^oC(O)NH₂, -NR^oC(S)NH₂, -NR^oC(O)NHR^o,
 -NR^oC(S)NHR^o, -NHC(O)NR^oR^o, -NHC(S)NR^oR^o, -NR^oC(O)NR^oR^o,
 -NR^oC(S)NR^oR^o, -NHS(O)₂NHR^o, -NR^oS(O)₂NH₂, -NR^oS(O)₂NHR^o,
 -NHS(O)₂NR^oR^o, -NR^oS(O)₂NR^oR^o, -NHR^o, -NR^oR^o, -R^d, -R^e, and -R^g;

optionally substituted cycloalkyl, optionally substituted heterocycloalkyl,
 optionally substituted aryl or optionally substituted heteroaryl, as R⁶⁸, R⁸¹, R¹¹², or
 optionally substituted 5-7 membered heterocycloalkyl as R⁷⁹ and R⁸⁰ combined
 with the nitrogen to which they are attached are cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl or 5-7 membered heterocycloalkyl, respectively, each of which is
 optionally substituted with one or more substituents selected from the group
 consisting of halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂,
 -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂,
 -OR^o, -SR^o, -OC(O)R^o, -OC(S)R^o, -C(O)R^o, -C(S)R^o, -C(O)OR^o, -C(S)OR^o,
 -S(O)R^o, -S(O)₂R^o, -C(O)NHR^o, -C(S)NHR^o, -C(O)NR^oR^o, -C(S)NR^oR^o,
 -S(O)₂NHR^o, -S(O)₂NR^oR^o, -C(NH)NHR^o, -C(NH)NR^oR^o, -NHC(O)R^o,
 -NHC(S)R^o, -NR^oC(O)R^o, -NR^oC(S)R^o, -NHS(O)₂R^o, -NR^oS(O)₂R^o,
 -NHC(O)NHR^o, -NHC(S)NHR^o, -NR^oC(O)NH₂, -NR^oC(S)NH₂, -NR^oC(O)NHR^o,
 -NR^oC(S)NHR^o, -NHC(O)NR^oR^o, -NHC(S)NR^oR^o, -NR^oC(O)NR^oR^o,
 -NR^oC(S)NR^oR^o, -NHS(O)₂NHR^o, -NR^oS(O)₂NH₂, -NR^oS(O)₂NHR^o,
 -NHS(O)₂NR^oR^o, -NR^oS(O)₂NR^oR^o, -NHR^o, -NR^oR^o, -R^d, -R^e, -R^f, and -R^g;

each R^o , R^p , and R^c are independently selected from the group consisting of R^d , R^e , R^f , and R^g , or R^p and R^c combine with the nitrogen to which they are attached to form a 5-7 membered heterocycloalkyl or a 5 or 7 membered nitrogen containing heteroaryl, wherein the 5-7 membered heterocycloalkyl or 5 or 7 membered nitrogen containing heteroaryl, respectively, are optionally substituted with one or more substituents selected from the group consisting of halogen, $-NO_2$, $-CN$, $-OH$, $-NH_2$, $-OR^u$, $-SR^u$, $-NHR^u$, $-NR^uR^u$, $-R^x$, and $-R^y$;

each R^d is independently C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^k$, $-SR^k$, $-OC(O)R^k$, $-OC(S)R^k$, $-C(O)R^k$, $-C(S)R^k$, $-C(O)OR^k$, $-C(S)OR^k$, $-S(O)R^k$, $-S(O)_2R^k$, $-C(O)NHR^k$, $-C(S)NHR^k$, $-C(O)NR^kR^k$, $-C(S)NR^kR^k$, $-S(O)_2NHR^k$, $-S(O)_2NR^kR^k$, $-C(NH)NHR^k$, $-C(NH)NR^mR^n$, $-NHC(O)R^k$, $-NHC(S)R^k$, $-NR^kC(O)R^k$, $-NR^kC(S)R^k$, $-NHS(O)_2R^k$, $-NR^kS(O)_2R^k$, $-NHC(O)NHR^k$, $-NHC(S)NHR^k$, $-NR^kC(O)NH_2$, $-NR^kC(S)NH_2$, $-NR^kC(O)NHR^k$, $-NR^kC(S)NHR^k$, $-NHC(O)NR^kR^k$, $-NHC(S)NR^kR^k$, $-NR^kC(O)NR^kR^k$, $-NR^kC(S)NR^kR^k$, $-NHS(O)_2NHR^k$, $-NR^kS(O)_2NH_2$, $-NR^kS(O)_2NHR^k$, $-NHS(O)_2NR^kR^k$, $-NR^kS(O)_2NR^kR^k$, $-NHR^k$, $-NR^kR^k$, $-R^i$, and $-R^j$;

each R^e is independently C_2 - C_6 alkenyl, wherein C_2 - C_6 alkenyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-C(O)OH$, $-C(S)OH$, $-C(O)NH_2$, $-C(S)NH_2$, $-S(O)_2NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-C(NH)NH_2$, $-OR^k$, $-SR^k$, $-OC(O)R^k$, $-OC(S)R^k$, $-C(O)R^k$, $-C(S)R^k$, $-C(O)OR^k$, $-C(S)OR^k$, $-S(O)R^k$, $-S(O)_2R^k$, $-C(O)NHR^k$, $-C(S)NHR^k$, $-C(O)NR^kR^k$, $-C(S)NR^kR^k$, $-S(O)_2NHR^k$, $-S(O)_2NR^kR^k$, $-C(NH)NHR^k$, $-C(NH)NR^mR^n$, $-NHC(O)R^k$, $-NHC(S)R^k$, $-NR^kC(O)R^k$, $-NR^kC(S)R^k$, $-NHS(O)_2R^k$, $-NR^kS(O)_2R^k$, $-NHC(O)NHR^k$, $-NHC(S)NHR^k$, $-NR^kC(O)NH_2$, $-NR^kC(S)NH_2$, $-NR^kC(O)NHR^k$, $-NR^kC(S)NHR^k$, $-NHC(O)NR^kR^k$, $-NHC(S)NR^kR^k$, $-NR^kC(O)NR^kR^k$, $-NR^kC(S)NR^kR^k$, $-NHS(O)_2NHR^k$, $-NR^kS(O)_2NH_2$, $-NR^kS(O)_2NHR^k$, $-NHS(O)_2NR^kR^k$, $-NR^kS(O)_2NR^kR^k$, $-NHR^k$, $-NR^kR^k$, $-R^h$, and $-R^j$;

each R^f is independently C_2 - C_6 alkynyl, wherein C_2 - C_6 alkynyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^k, -SR^k, -OC(O)R^k, -OC(S)R^k, -C(O)R^k, -C(S)R^k, -C(O)OR^k, -C(S)OR^k, -S(O)R^k, -S(O)₂R^k, -C(O)NHR^k, -C(S)NHR^k, -C(O)NR^kR^k, -C(S)NR^kR^k, -S(O)₂NHR^k, -S(O)₂NR^kR^k, -C(NH)NHR^k, -C(NH)NR^mRⁿ, -NHC(O)R^k, -NHC(S)R^k, -NR^kC(O)R^k, -NR^kC(S)R^k, -NHS(O)₂R^k, -NR^kS(O)₂R^k, -NHC(O)NHR^k, -NHC(S)NHR^k, -NR^kC(O)NH₂, -NR^kC(S)NH₂, -NR^kC(O)NHR^k, -NR^kC(S)NHR^k, -NHC(O)NR^kR^k, -NHC(S)NR^kR^k, -NR^kC(O)NR^kR^k, -NR^kC(S)NR^kR^k, -NHS(O)₂NHR^k, -NR^kS(O)₂NH₂, -NR^kS(O)₂NHR^k, -NHS(O)₂NR^kR^k, -NR^kS(O)₂NR^kR^k, -NHR^k, -NR^kR^k, -R^h, and -R^j;

each R^g is independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, respectively, are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^k, -SR^k, -OC(O)R^k, -OC(S)R^k, -C(O)R^k, -C(S)R^k, -C(O)OR^k, -C(S)OR^k, -S(O)R^k, -S(O)₂R^k, -C(O)NHR^k, -C(S)NHR^k, -C(O)NR^kR^k, -C(S)NR^kR^k, -S(O)₂NHR^k, -S(O)₂NR^kR^k, -C(NH)NHR^k, -C(NH)NR^mRⁿ, -NHC(O)R^k, -NHC(S)R^k, -NR^kC(O)R^k, -NR^kC(S)R^k, -NHS(O)₂R^k, -NR^kS(O)₂R^k, -NHC(O)NHR^k, -NHC(S)NHR^k, -NR^kC(O)NH₂, -NR^kC(S)NH₂, -NR^kC(O)NHR^k, -NR^kC(S)NHR^k, -NHC(O)NR^kR^k, -NHC(S)NR^kR^k, -NR^kC(O)NR^kR^k, -NR^kC(S)NR^kR^k, -NHS(O)₂NHR^k, -NR^kS(O)₂NH₂, -NR^kS(O)₂NHR^k, -NHS(O)₂NR^kR^k, -NR^kS(O)₂NR^kR^k, -NHR^k, -NR^kR^k, -R^h, -Rⁱ, and -R^j;

R^k , R^m , and R^n at each occurrence are independently selected from the group consisting of R^h , R^i , and R^j , or R^m and R^n combine with the nitrogen to which they are attached form a 5-7 membered heterocycloalkyl or a 5 or 7 membered nitrogen containing heteroaryl, wherein the 5-7 membered heterocycloalkyl or 5 or 7 membered nitrogen containing heteroaryl, respectively, are optionally substituted

with one or more substituents selected from the group consisting of halogen, -NO₂, -CN, -OH, -NH₂, OR^u, -SR^u, -NHR^u, -NR^uR^u, -R^x, and -R^y;

each R^h is independently C₁-C₆ alkyl optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^r, -SR^r, -OC(O)R^r, -OC(S)R^r, -C(O)R^r, -C(S)R^r, -C(O)OR^r, -C(S)OR^r, -S(O)R^r, -S(O)₂R^r, -C(O)NHR^r, -C(S)NHR^r, -C(O)NR^rR^r, -C(S)NR^rR^r, -S(O)₂NHR^r, -S(O)₂NR^rR^r, -C(NH)NHR^r, -C(NH)NR^sR^t, -NHC(O)R^r, -NHC(S)R^r, -NR^rC(O)R^r, -NR^rC(S)R^r, -NHS(O)₂R^r, -NR^rS(O)₂R^r, -NHC(O)NHR^r, -NHC(S)NHR^r, -NR^rC(O)NH₂, -NR^rC(S)NH₂, -NR^rC(O)NHR^r, -NR^rC(S)NHR^r, -NHC(O)NR^rR^r, -NHC(S)NR^rR^r, -NR^rC(O)NR^rR^r, -NR^rC(S)NR^rR^r, -NHS(O)₂NHR^r, -NR^rS(O)₂NH₂, -NR^rS(O)₂NHR^r, -NHS(O)₂NR^rR^r, -NR^rS(O)₂NR^rR^r, -NHR^r, -NR^rR^r, -Rⁱ, and -R^j;

each Rⁱ is independently selected from the group consisting of C₂-C₆ alkenyl and C₂-C₆ alkynyl, wherein C₂-C₆ alkenyl or C₂-C₆ alkynyl, respectively, are optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^r, -SR^r, -OC(O)R^r, -OC(S)R^r, -C(O)R^r, -C(S)R^r, -C(O)OR^r, -C(S)OR^r, -S(O)R^r, -S(O)₂R^r, -C(O)NHR^r, -C(S)NHR^r, -C(O)NR^rR^r, -C(S)NR^rR^r, -S(O)₂NHR^r, -S(O)₂NR^rR^r, -C(NH)NHR^r, -C(NH)NR^sR^t, -NHC(O)R^r, -NHC(S)R^r, -NR^rC(O)R^r, -NR^rC(S)R^r, -NHS(O)₂R^r, -NR^rS(O)₂R^r, -NHC(O)NHR^r, -NHC(S)NHR^r, -NR^rC(O)NH₂, -NR^rC(S)NH₂, -NR^rC(O)NHR^r, -NR^rC(S)NHR^r, -NHC(O)NR^rR^r, -NHC(S)NR^rR^r, -NR^rC(O)NR^rR^r, -NR^rC(S)NR^rR^r, -NHS(O)₂NHR^r, -NR^rS(O)₂NH₂, -NR^rS(O)₂NHR^r, -NHS(O)₂NR^rR^r, -NR^rS(O)₂NR^rR^r, -NHR^r, -NR^rR^r, and -R^j;

each R^j is independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, respectively, are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, -C(O)OH, -C(S)OH, -C(O)NH₂, -C(S)NH₂, -S(O)₂NH₂, -NHC(O)NH₂, -NHC(S)NH₂, -NHS(O)₂NH₂, -C(NH)NH₂, -OR^r, -SR^r, -OC(O)R^r, -OC(S)R^r,

-C(O)R^r, -C(S)R^r, -C(O)OR^r, -C(S)OR^r, -S(O)R^r, -S(O)₂R^r, -C(O)NHR^r,
 -C(S)NHR^r, -C(O)NR^rR^r, -C(S)NR^rR^r, -S(O)₂NHR^r, -S(O)₂NR^rR^r, -C(NH)NHR^r,
 -C(NH)NR^sR^t, -NHC(O)R^r, -NHC(S)R^r, -NR^rC(O)R^r, -NR^rC(S)R^r, -NHS(O)₂R^r,
 -NR^rS(O)₂R^r, -NHC(O)NHR^r, -NHC(S)NHR^r, -NR^rC(O)NH₂, -NR^rC(S)NH₂,
 -NR^rC(O)NHR^r, -NR^rC(S)NHR^r, -NHC(O)NR^rR^r, -NHC(S)NR^rR^r,
 -NR^rC(O)NR^rR^r, -NR^rC(S)NR^rR^r, -NHS(O)₂NHR^r, -NR^rS(O)₂NH₂,
 -NR^rS(O)₂NHR^r, -NHS(O)₂NR^rR^r, -NR^rS(O)₂NR^rR^r, -NHR^r, -NR^rR^r,
 cycloalkylamino, and -R^x;

R^r, R^s, and R^t at each occurrence are independently selected from the group consisting of C₁-C₆ alkyl, C₃₋₆ alkenyl, C₃₋₆ alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl; wherein C₁-C₆ alkyl is optionally substituted with one or more substituents selected from the group consisting of -R^y, fluoro, -OH, -NH₂, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the C₁-C₆ alkyl carbon bound to any O, S, or N, of -OR^r, -SR^r, -C(O)OR^r, -C(S)OR^r, -C(O)NHR^r, -C(S)NHR^r, -C(O)NR^rR^r, -C(S)NR^rR^r, -S(O)₂NHR^r, -S(O)₂NR^rR^r, -C(NH)NHR^r, -NR^rC(O)R^r, -NR^rC(S)R^r, -NR^rS(O)₂R^r, -NHC(O)NHR^r, -NHC(S)NHR^r, -NR^rC(O)NH₂, -NR^rC(S)NH₂, -NR^rC(O)NHR^r, -NR^rC(S)NHR^r, -NHC(O)NR^rR^r, -NHC(S)NR^rR^r, -NR^rC(O)NR^rR^r, -NR^rC(S)NR^rR^r, -NHS(O)₂NHR^r, -NR^rS(O)₂NH₂, -NR^rS(O)₂NHR^r, -NHS(O)₂NR^rR^r, -NR^rS(O)₂NR^rR^r, -NHR^r, or -NR^rR^r is selected from the group consisting of fluoro and -R^y; and wherein C₃₋₆ alkenyl or C₃₋₆ alkynyl, respectively, are optionally substituted with one or more substituents selected from the group consisting of -R^y, fluoro, C₁-C₆ alkyl, fluoro substituted C₁-C₆ alkyl, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the C₃₋₆ alkenyl or C₃₋₆ alkynyl carbon bound to any O, S, or N, of -OR^r, -SR^r, -C(O)OR^r, -C(S)OR^r, -C(O)NHR^r, -C(S)NHR^r, -C(O)NR^rR^r, -C(S)NR^rR^r, -S(O)₂NHR^r, -S(O)₂NR^rR^r, -C(NH)NHR^r, -NR^rC(O)R^r, -NR^rC(S)R^r, -NR^rS(O)₂R^r, -NHC(O)NHR^r, -NHC(S)NHR^r, -NR^rC(O)NH₂, -NR^rC(S)NH₂, -NR^rC(O)NHR^r, -NR^rC(S)NHR^r, -NHC(O)NR^rR^r, -NHC(S)NR^rR^r, -NR^rC(O)NR^rR^r, -NR^rC(S)NR^rR^r,

-NHS(O)₂NHR^f, -NR^fS(O)₂NH₂, -NR^fS(O)₂NHR^f, -NHS(O)₂NR^fR^f, -NR^fS(O)₂NR^fR^f, -NHR^f, or -NR^fR^f is selected from the group consisting of fluoro, C₁-C₆ alkyl, fluoro substituted C₁-C₆ alkyl, and -R^y; and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, respectively, are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, C₁-C₆ alkyl, fluoro substituted C₁-C₆ alkyl, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, or R^s and R^t combine with the nitrogen to which they are attached form a 5-7 membered heterocycloalkyl or a 5 or 7 membered nitrogen containing heteroaryl, wherein the 5-7 membered heterocycloalkyl or 5 or 7 membered nitrogen containing heteroaryl, respectively, are optionally substituted with one or more substituents selected from the group consisting of halogen, -NO₂, -CN, -OH, -NH₂, OR^u, -SR^u, -NHR^u, -NR^uR^u, -R^x, and -R^y;

each R^u is independently selected from the group consisting of C₁-C₆ alkyl, C₃-₆ alkenyl, C₃-₆ alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein C₁-C₆ alkyl is optionally substituted with one or more substituents selected from the group consisting of -R^y, fluoro, -OH, -NH₂, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the C₁-C₆ alkyl carbon bound to the O of -OR^u, S of -SR^u, or N of -NHR^u is fluoro or -R^y; and wherein C₃-₆ alkenyl or C₃-₆ alkynyl, respectively, are optionally substituted with one or more substituents selected from the group consisting of -R^y, fluoro, -OH, -NH₂, C₁-C₆ alkyl, fluoro substituted C₁-C₆ alkyl, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the C₃-₆ alkenyl or C₃-₆ alkynyl carbon bound to the O of -OR^u, S of -SR^u, or N of -NHR^u is fluoro, C₁-C₆ alkyl, fluoro substituted C₁-C₆ alkyl, or -R^y; and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, respectively, are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, C₁-C₆ alkyl, fluoro substituted C₁-C₆ alkyl, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆

alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

each R^x is selected from the group consisting of C₁-C₆ alkyl, C₂-C₆ alkenyl and C₂-C₆ alkynyl, wherein C₁-C₆ alkyl is optionally substituted with one or more substituents selected from the group consisting of -R^y, fluoro, -OH, -NH₂, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; and wherein C₂-C₆ alkenyl or C₂-C₆ alkynyl, respectively, are optionally substituted with one or more substituents selected from the group consisting of -R^y, fluoro, -OH, -NH₂, C₁-C₆ alkyl, fluoro substituted C₁-C₆ alkyl, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

each R^y is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, respectively, are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH₂, -NO₂, -CN, C₁-C₆ alkyl, fluoro substituted C₁-C₆ alkyl, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

at each occurrence, **alkenyl, by itself or as part of another substituent,** is a straight or branched chain hydrocarbon having at least one carbon-to-carbon double bond;

at each occurrence, **alkynyl, by itself or as part of another substituent,** is a straight or branched chain hydrocarbon having at least one carbon-to-carbon triple bond;

at each occurrence, **cycloalkyl, by itself or as part of another substituent,** is a saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring system of 3-10 ring members per ring; and

at each occurrence, **heterocycloalkyl, by itself or as part of another substituent,** is a saturated or unsaturated non-aromatic 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.

2. The compound of claim 1, wherein:

R^{81} is selected from the group consisting of hydrogen, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -CN, -S(O)₂NH₂, -C(O)NH₂, -OR⁶⁸, -SR⁶⁸, -NR⁶⁹R⁶⁸, -C(O)R⁶⁸, -C(S)R⁶⁸, -C(O)NR⁶⁹R⁶⁸, -S(O)₂NR⁶⁹R⁶⁸, -NR⁶⁹C(O)R⁶⁸, -NR⁶⁹S(O)₂R⁶⁸, -S(O)R⁶⁸, and -S(O)₂R⁶⁸.

3. The compound of claim 1, wherein:

C_1 - C_6 alkyl as R^{68} , R^{69} , R^{79} , R^{80} , or R^{81} , C_2 - C_6 alkyl as R^{112} , C_2 - C_6 alkenyl as R^{68} or R^{81} , or C_2 - C_6 alkynyl as R^{68} or R^{81} are optionally substituted with 1, 2, or 3 groups or substituents selected from the group consisting of fluoro, -NO₂, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -OC(O)R^{1a}, -OC(S)R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -C(O)OR^{1a}, -C(S)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -C(NH)NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -NR^{1a}C(O)NR^{1a}R^{1a}, -NR^{1a}C(S)NR^{1a}R^{1a}, -NR^{1a}S(O)₂NR^{1a}R^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

cycloalkyl, heterocycloalkyl, aryl or heteroaryl, as R^{68} , R^{81} , R^{112} , or a substituent of C_1 - C_6 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl; or 5-7 membered heterocycloalkyl as R^{79} and R^{80} combined with the nitrogen to which they are attached, are optionally substituted with 1, 2, or 3 groups or substituents selected from the group consisting of halogen, -NO₂, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -OC(O)R^{1a}, -OC(S)R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -C(O)OR^{1a}, -C(S)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -C(NH)NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -NR^{1a}C(O)NR^{1a}R^{1a}, -NR^{1a}C(S)NR^{1a}R^{1a}, -NR^{1a}S(O)₂NR^{1a}R^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, -R^{1b}, and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with 1, 2 or 3 groups or substituents selected from the group consisting of fluoro, -OH, -NH₂, C_1 - C_6 alkoxy, fluoro substituted C_1 - C_6 alkoxy, C_1 - C_6

alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and -R^{1b};

R^{1a} is selected from the group consisting of hydrogen, -R^{1b}, and C₁-C₆ alkyl, provided, however, that hydrogen is not bound to any of C(S), C(O), S(O), or S(O)₂ of -OC(O)R^{1a}, -OC(S)R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -S(O)R^{1a}, or -S(O)₂R^{1a}, wherein C₁-C₆ alkyl is optionally substituted with 1, 2 or 3 groups or substituents selected from the group consisting of fluoro, -OH, -NH₂, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and -R^{1b}, provided, however, that any substitution of the alkyl carbon bound to O, S, or N of -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -C(O)OR^{1a}, -C(S)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -C(NH)NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -NR^{1a}C(O)NR^{1a}R^{1a}, -NR^{1a}C(S)NR^{1a}R^{1a}, or -NR^{1a}S(O)₂NR^{1a}R^{1a}, is fluoro or -R^{1b}; and

R^{1b} is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1, 2 or 3 groups or substituents selected from the group consisting of halogen, -CN, -OH, -NH₂, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

4. The compound of claim 1, wherein:

C₁-C₆ alkyl as R⁶⁸, R⁶⁹, R⁷⁹, R⁸⁰, or R⁸¹, C₂-C₆ alkyl as R¹¹², C₂-C₆ alkenyl as R⁶⁸ or R⁸¹, or C₂-C₆ alkynyl as R⁶⁸ or R⁸¹ are optionally substituted with 1, 2, or 3 substituents selected from the group consisting of fluoro, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, cycloalkyl, heterocycloalkyl, aryl and heteroaryl; and

cycloalkyl, heterocycloalkyl, aryl or heteroaryl, as R⁶⁸, R⁸¹, R¹¹², or a substituent of C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl; or 5-7 membered heterocycloalkyl as R⁷⁹ and R⁸⁰ combined with the nitrogen to which they are attached, are optionally substituted with 1, 2, or 3 substituents selected from the

group consisting of halogen, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1a}, -C(O)R^{1a}, -C(S)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1a}R^{1a}, -C(S)NR^{1a}R^{1a}, -S(O)₂NR^{1a}R^{1a}, -NR^{1a}C(O)R^{1a}, -NR^{1a}C(S)R^{1a}, -NR^{1a}S(O)₂R^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, -R^{1b}, and C₁-C₆ alkyl, wherein C₁-C₆ alkyl is optionally substituted with 1, 2 or 3 substituents selected from the group consisting of fluoro, -OH, -NH₂, C₁-C₆ alkoxy, fluoro substituted C₁-C₆ alkoxy, C₁-C₆ alkylthio, fluoro substituted C₁-C₆ alkylthio, mono-alkylamino, di-alkylamino, and -R^{1b}.

5. The compound of claim 1, wherein R¹¹² is optionally substituted C₂₋₆ alkyl.

6. The compound of claim 1, wherein R¹¹² is -NR⁷⁹R⁸⁰.

7. The compound of claim 1, wherein R¹¹² is optionally substituted aryl.

8. The compound of claim 1, wherein R¹¹² is optionally substituted heteroaryl.

9. The compound of claim 1, wherein:

R⁸¹ is selected from the group consisting of hydrogen; halogen; C₁₋₆ alkyl optionally substituted with carboxylic acid; C₂₋₆ alkenyl optionally substituted with carboxylic acid; C₁₋₆ alkoxy optionally substituted with methoxy or diethylamine; carboxylic acid; carboxylic acid methyl ester; carboxylic acid ethylamide; 4-methyl-piperidin-1-yl; 4-methyl-piperazin-1-yl; morpholin-4-yl; phenyl-amino; phenyl optionally substituted with halogen, -CN, optionally fluoro substituted C₁₋₆ alkyl, dimethylamine, methoxy, carboxylic acid, carboxylic acid amide, carboxylic acid-dimethyl amide, morpholine-4-carbonyl, morpholine, morpholine-4-methyl, or 2-methoxy-ethoxy; pyridinyl optionally substituted with methoxy, morpholine, or 4-methyl-piperazin-1-yl; 4-methyl-1H-imidazol-2-yl; and N-methyl-pyrazolyl;

R⁸³ is selected from the group consisting of hydrogen, fluoro and chloro;

R¹¹² is selected from the group consisting of C₂₋₆ alkyl; phenyl optionally substituted with -CN, -NO₂, acetamide, halogen, optionally fluoro substituted C₁₋₆

alkyl, optionally fluoro substituted C₁₋₆ alkoxy, or oxazolyl; 2,3-dihydro-benzo[1,4]dioxin-6-yl; methyl substituted thiazole, methyl substituted imidazole, thiophene optionally substituted with methyl, oxazole, isoxazole, or pyridine; furan substituted with methyl or carboxylic acid methyl ester; benzothiazol-6-yl; benzo[b]thiophen-2-yl; piperidin-1-yl; and dimethylamine.

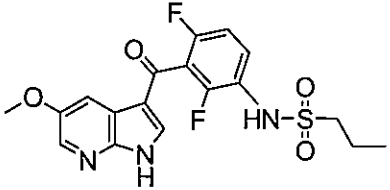
10. The compound of claim 9, wherein R¹¹² is C₂₋₆ alkyl.

11. The compound of claim 9, wherein R¹¹² is piperidin-1-yl or dimethylamine.

12. The compound of claim 9, wherein R¹¹² is selected from the group consisting of 2,3-dihydro-benzo[1,4]dioxin-6-yl; and phenyl optionally substituted with -CN, -NO₂, acetamide, halogen, optionally fluoro substituted C₁₋₆ alkyl, optionally fluoro substituted C₁₋₆ alkoxy, or oxazolyl.

13. The compound of claim 9, wherein R¹¹² is selected from the group consisting of methyl substituted thiazole; methyl substituted imidazole; thiophene optionally substituted with methyl, oxazole, isoxazole, or pyridine; furan substituted with methyl or carboxylic acid methyl ester; benzothiazol-6-yl; and benzo[b]thiophen-2-yl.

14. The compound of claim 1, wherein the compound is selected from the group consisting of:

Name	Structure
Propane-1-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	

Propane-1-sulfonic acid [3-(5-ethoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
Propane-1-sulfonic acid [2-fluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid {3-[5-(2-diethylaminoethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluorophenyl}-amide	
Butane-1-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	

and pharmaceutically acceptable salts thereof.

15. The compound of claim 1, wherein the compound is selected from the group consisting of:

Name	Structure
Propane-1-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid [2,4-difluoro-3-(5-isopropenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid [2,4-difluoro-3-(5-isopropyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	

Propane-1-sulfonic acid [4-chloro-2-fluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid [2-fluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
3-3-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl-propionic acid	
Butane-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	
Propane-1-sulfonic acid [2,4-difluoro-3-(5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid [4-chloro-3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide	

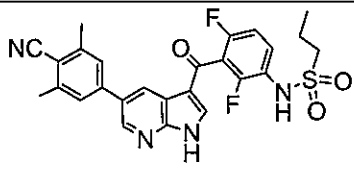
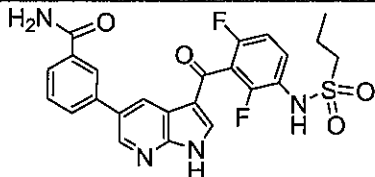
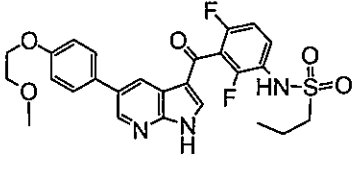
and pharmaceutically acceptable salts thereof.

16. The compound of claim 1, wherein the compound is selected from the group consisting of:

Name	Structure
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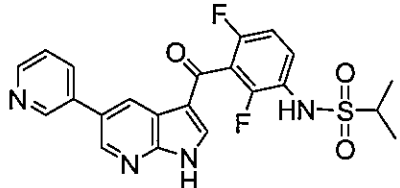
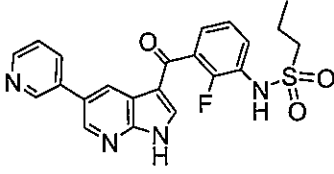
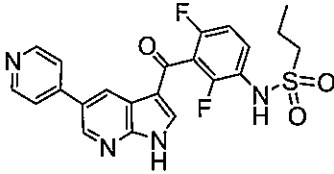
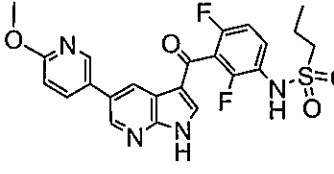
Propane-1-sulfonic acid [4-chloro-2-fluoro-3-(5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid [2,4-difluoro-3-(5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid {3-[5-(4-dimethylamino-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(3-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	
Propane-1-sulfonic acid {3-[5-(3-dimethylamino-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide	
Propane-1-sulfonic acid [2-fluoro-3-(5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(3-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	

Propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	
Propane-1-sulfonic acid {3-[5-(3-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide	
3-{3-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-benzoic acid	
4-{3-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-benzamide	
4-{3-[2,6-Difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-N,N-dimethyl-benzamide	
Propane-1-sulfonic acid (2,4-difluoro-3-{5-[4-(morpholine-4-carbonyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl}-phenyl)-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(3-morpholin-4-yl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(3-morpholin-4-ylmethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	

Propane-1-sulfonic acid {3-[5-(4-cyano-3,5-dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide	
3-{3-[2,6-difluoro-3-(propane-1-sulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-benzamide	
Propane-1-sulfonic acid (2,4-difluoro-3-{5-[4-(2-methoxy-ethoxy)-phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl}-phenyl)-amide	

and pharmaceutically acceptable salts thereof.

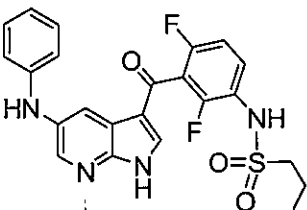
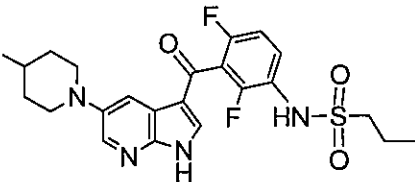
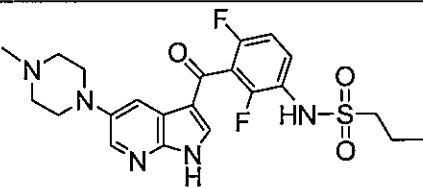
17. The compound of claim 1, wherein the compound is selected from the group consisting of:

Name	Structure
Propane-2-sulfonic acid [2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid [2-fluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid [2,4-difluoro-3-(5-pyridin-4-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(6-methoxy-pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	

phenyl}-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(6-morpholin-4-yl-pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	
Propane-1-sulfonic acid (2,4-difluoro-3-{5-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl}-phenyl)-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	

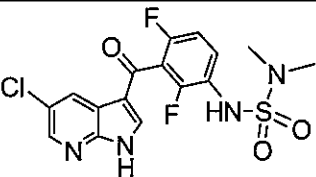
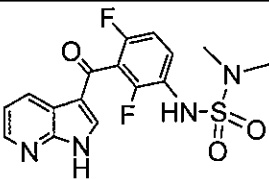
and pharmaceutically acceptable salts thereof.

18. The compound of claim 1, wherein the compound is selected from the group consisting of:

Name	Structure
Propane-1-sulfonic acid [2,4-difluoro-3-(5-phenylamino-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-methyl-piperidin-1-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	
Propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-methyl-piperazin-1-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide	

and pharmaceutically acceptable salts thereof.

19. The compound of claim 1, wherein the compound is selected from the group consisting of:

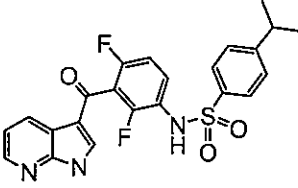
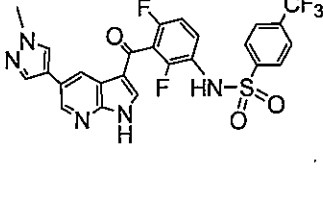
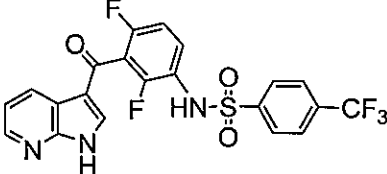
Name	Structure
Dimethylamine-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
Dimethylamine-1-sulfonic acid [3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	

Piperidine-1-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Piperidine-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	
Dimethylamine-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide	

and pharmaceutically acceptable salts thereof.

20. The compound of claim 1, wherein the compound is selected from the group consisting of:

Name	Structure
N-[3-(5-Ethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide	
N-(2,4-Difluoro-3-{5-[4-(2-methoxy-ethoxy)-phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonyl}-phenyl)-4-trifluoromethyl-benzenesulfonamide	
N-{2,4-difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide	

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-isopropylbenzenesulfonamide	
N-{2,4-Difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethylbenzenesulfonamide	
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethylbenzenesulfonamide	

and pharmaceutically acceptable salts thereof.

21. The compound of claim 1, wherein the compound is selected from the group consisting of:

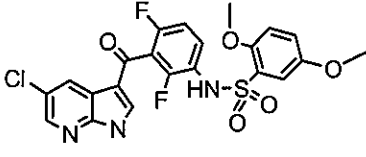
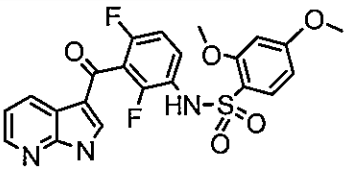
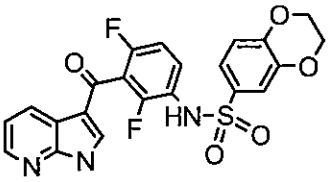
Name	Structure
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-3-fluoro-4-methylbenzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-4-methylbenzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-benzenesulfonamide	
N-[2,4-Difluoro-3-(5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-2-methylbenzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-5-fluoro-2-methylbenzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-3-methylbenzenesulfonamide	

N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2-methyl-benzenesulfonamide	
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-methyl-benzenesulfonamide	
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide	
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-5-fluoro-2-methyl-benzenesulfonamide	
N-[2,4-Difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl] benzenesulfonamide	

and pharmaceutically acceptable salts thereof.

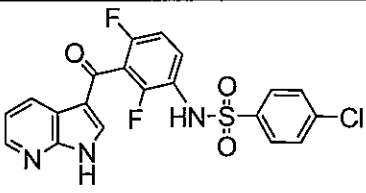
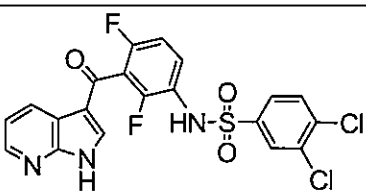
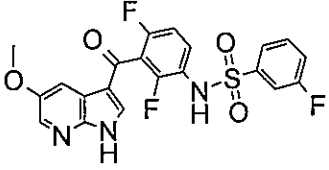
22. The compound of claim 1, wherein the compound is selected from the group consisting of:

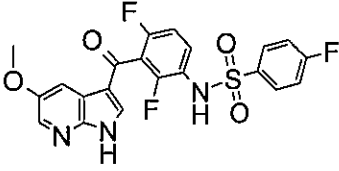
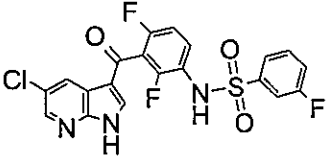
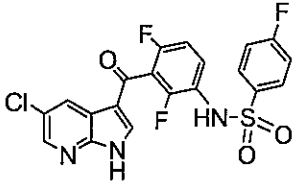
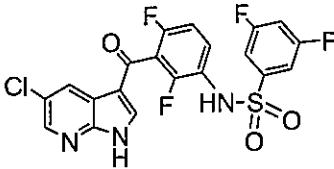
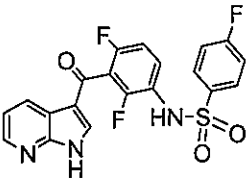
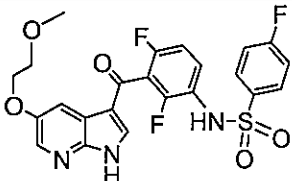
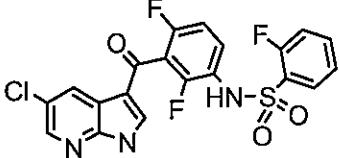
Name	Structure
N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl) phenyl]-3-methoxy-benzenesulfonamide	
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-methoxy-benzenesulfonamide	
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3,4-dimethoxy-benzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-methoxy-benzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-methoxy-benzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,4-dimethoxy-benzenesulfonamide	
2,3-Dihydro-benzo[1,4]dioxine-6-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-	

2,4-difluoro-phenyl]-amide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,5-dimethoxy-benzenesulfonamide	
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,4-dimethoxy-benzenesulfonamide	
2,3-Dihydro-benzo[1,4]dioxine-6-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	

and pharmaceutically acceptable salts thereof.

23. The compound of claim 1, wherein the compound is selected from the group consisting of:

Name	Structure
4-Chloro-N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide	
3,4-Dichloro-N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide	
N-[2,4-Difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-	

fluoro-benzenesulfonamide	
N-[2,4-Difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-fluoro-benzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-fluoro-benzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-fluoro-benzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3,5-difluoro-benzenesulfonamide	
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-fluoro-benzenesulfonamide	
N-{2,4-Difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-fluoro-benzenesulfonamide	
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2-fluoro-benzenesulfonamide	

and pharmaceutically acceptable salts thereof.

24. The compound of claim 1, wherein the compound is selected from the group consisting of:

Name	Structure
N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-4-oxazol-5-ylbenzenesulfonamide	
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-oxazol-5-ylbenzenesulfonamide	
N-{4-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenylsulfamoyl]-phenyl}-acetamide	
N-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-nitrobenzenesulfonamide	
N-{4-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenylsulfamoyl]-phenyl}-acetamide	
2-Cyano-N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide	
3-Cyano-N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide	

and pharmaceutically acceptable salts thereof.

25. The compound of claim 1, wherein the compound is selected from the group consisting of:

Name	Structure
Thiophene-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
Benzo[b]thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
5-Pyridin-2-yl-thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
Thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
2,5-Dimethyl-thiophene-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
5-Isioxazol-5-yl-thiophene-2-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	

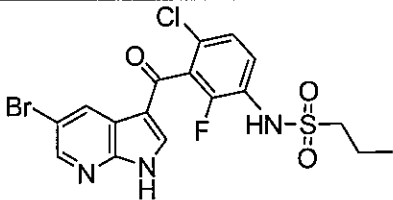
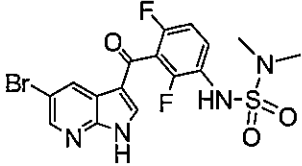
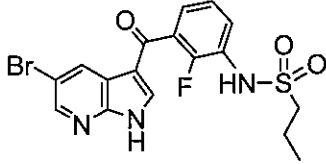
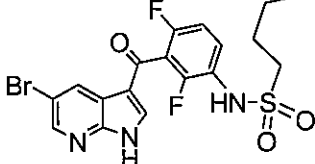
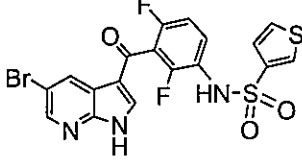
2,5-Dimethyl-thiophene-3-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
2,4-Dimethyl-thiazole-5-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
Benzothiazole-6-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
2,4-Dimethyl-thiazole-5-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
5-Oxazol-5-yl-thiophene-2-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	
1,2-Dimethyl-1H-imidazole-4-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
5-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenylsulfamoyl]-furan-2-carboxylic acid methyl ester	
5-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenylsulfamoyl]-2-methyl-furan-3-carboxylic acid methyl ester	

2,5-Dimethyl-furan-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
5-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenylsulfamoyl]-furan-2-carboxylic acid methyl ester	
5-[2,4-Difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenylsulfamoyl]-2-methyl-furan-3-carboxylic acid methyl ester	
2,5-Dimethyl-furan-3-sulfonic acid [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide	

and pharmaceutically acceptable salts thereof.

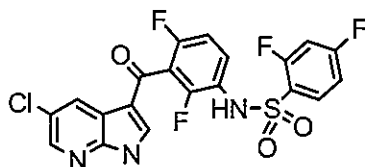
26. The compound of claim 1, wherein said compound is selected from the group consisting of:

Name	Structure
Propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide	
N-[3-(5-Bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-benzenesulfonamide	

Propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-chloro-2-fluoro-phenyl]-amide	
Dimethylamine-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	
Propane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide	
Butane-1-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	
Thiophene-3-sulfonic acid [3-(5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide	

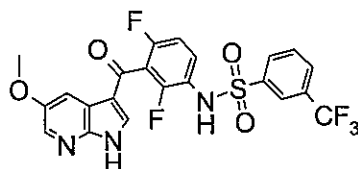
and pharmaceutically acceptable salts thereof.

27. The compound of claim 1, wherein the compound is N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2,4-difluorobenzenesulfonamide having the structure:



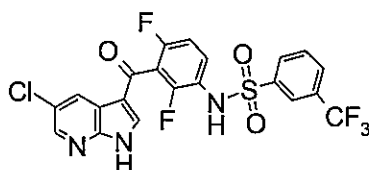
or a pharmaceutically acceptable salt thereof.

28. The compound of claim 1, wherein the compound is N-[2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-3-trifluoromethylbenzenesulfonamide having the structure:



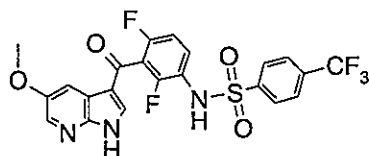
or a pharmaceutically acceptable salt thereof.

29. The compound of claim 1, wherein the compound is N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-3-trifluoromethylbenzenesulfonamide having the structure:



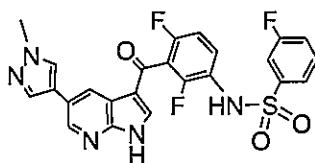
or a pharmaceutically acceptable salt thereof.

30. The compound of claim 1, wherein the compound is N-[2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethylbenzenesulfonamide having the structure:



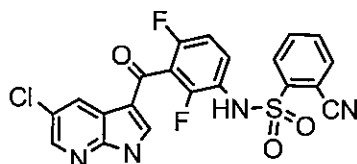
or a pharmaceutically acceptable salt thereof.

31. The compound of claim 1, wherein the compound is N-{2,4-difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-3-fluorobenzenesulfonamide having the structure:



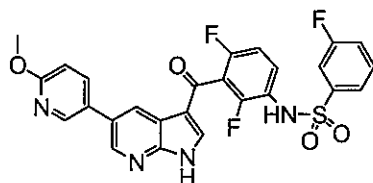
or a pharmaceutically acceptable salt thereof.

32. The compound of claim 1, wherein the compound is N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-2-cyano-benzenesulfonamide having the structure:



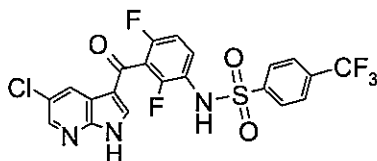
or a pharmaceutically acceptable salt thereof.

33. The compound of claim 1, wherein the compound is N-{2,4-difluoro-3-[5-(6-methoxy-pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-3-fluoro-benzenesulfonamide having the structure:



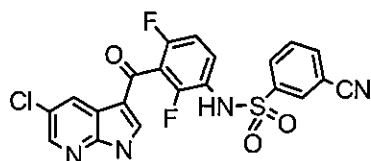
or a pharmaceutically acceptable salt thereof.

34. The compound of claim 1, wherein the compound is N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide having the structure:



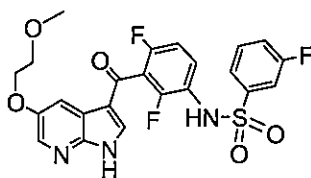
or a pharmaceutically acceptable salt thereof.

35. The compound of claim 1, wherein the compound is N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-cyano-benzenesulfonamide having the structure:



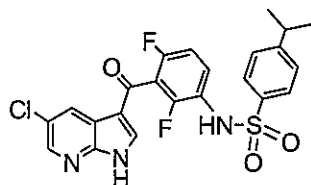
or a pharmaceutically acceptable salt thereof.

36. The compound of claim 1, wherein the compound is N-{2,4-difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-3-fluorobenzenesulfonamide having the structure:



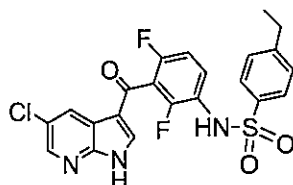
or a pharmaceutically acceptable salt thereof.

37. The compound of claim 1, wherein the compound is N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-isopropylbenzenesulfonamide having the structure:



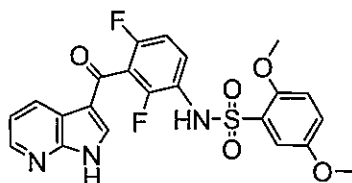
or a pharmaceutically acceptable salt thereof.

38. The compound of claim 1, wherein the compound is N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-ethylbenzenesulfonamide having the structure:



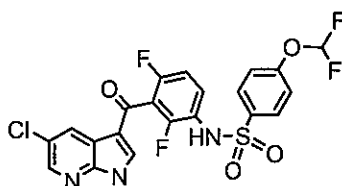
or a pharmaceutically acceptable salt thereof.

39. The compound of claim 1, wherein the compound is N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-2,5-dimethoxybenzenesulfonamide having the structure:



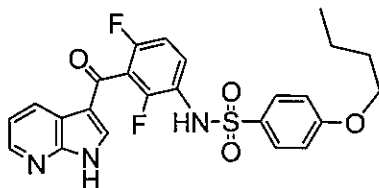
or a pharmaceutically acceptable salt thereof.

40. The compound of claim 1, wherein the compound is N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-difluoromethoxybenzenesulfonamide having the structure:



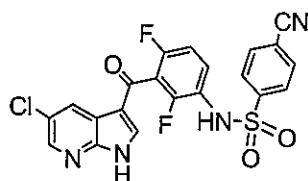
or a pharmaceutically acceptable salt thereof.

41. The compound of claim 1, wherein the compound is 4-butoxy-N-[2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-benzenesulfonamide having the structure:



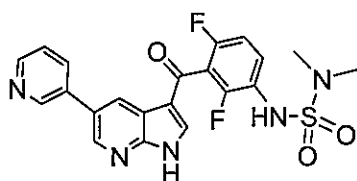
or a pharmaceutically acceptable salt thereof.

42. The compound of claim 1, wherein the compound is N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-cyano-benzenesulfonamide having the structure:



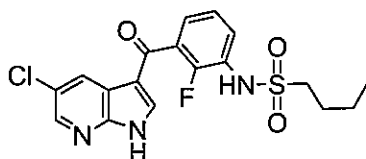
or a pharmaceutically acceptable salt thereof.

43. The compound of claim 1, wherein the compound is dimethylamine-1-sulfonic acid [3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide having the structure:



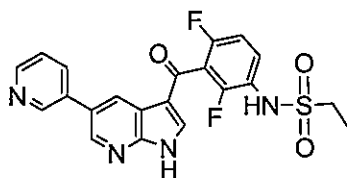
or a pharmaceutically acceptable salt thereof.

44. The compound of claim 1, wherein the compound is butane-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluoro-phenyl]-amide having the structure:



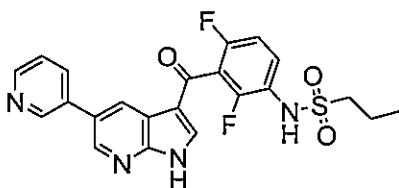
or a pharmaceutically acceptable salt thereof.

45. The compound of claim 1, wherein the compound is N-[2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-ethanesulfonamide having the structure:



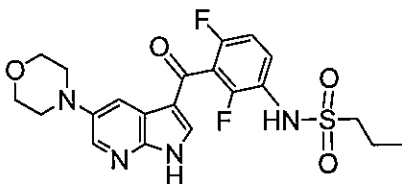
or a pharmaceutically acceptable salt thereof.

46. The compound of claim 1, wherein the compound is propane-1-sulfonic acid [2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide having the structure:



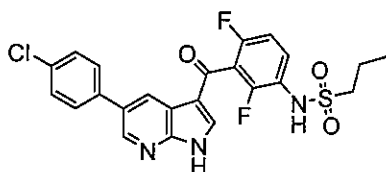
or a pharmaceutically acceptable salt thereof.

47. The compound of claim 1, wherein the compound is propane-1-sulfonic acid [2,4-difluoro-3-(5-morpholin-4-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide having the structure:



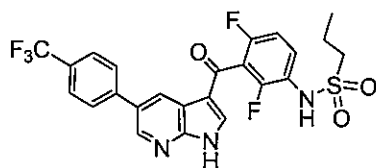
or a pharmaceutically acceptable salt thereof.

48. The compound of claim 1, wherein the compound is propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide having the structure:



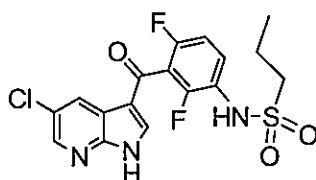
or a pharmaceutically acceptable salt thereof.

49. The compound of claim 1, wherein the compound is propane-1-sulfonic acid {2,4-difluoro-3-[5-(4-trifluoromethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide having the structure:



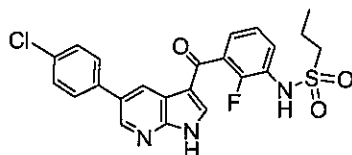
or a pharmaceutically acceptable salt thereof.

50. The compound of claim 1, wherein the compound is propane-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl]-amide having the structure:



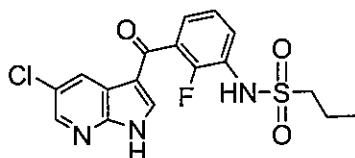
or a pharmaceutically acceptable salt thereof.

51. The compound of claim 1, wherein the compound is propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2-fluoro-phenyl}-amide having the structure:



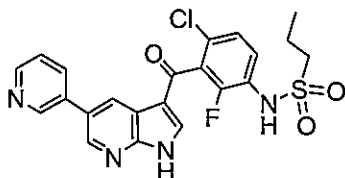
or a pharmaceutically acceptable salt thereof.

52. The compound of claim 1, wherein the compound is propane-1-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-fluorophenyl]-amide having the structure:



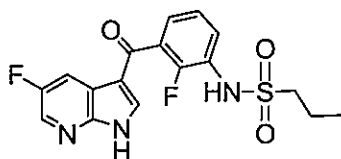
or a pharmaceutically acceptable salt thereof.

53. The compound of claim 1, wherein the compound is propane-1-sulfonic acid [4-chloro-2-fluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide having the structure:



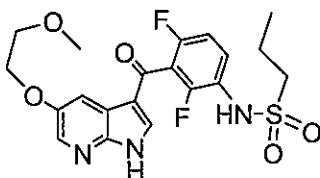
or a pharmaceutically acceptable salt thereof.

54. The compound of claim 1, wherein the compound is propane-1-sulfonic acid [2-fluoro-3-(5-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide having the structure:



or a pharmaceutically acceptable salt thereof.

55. The compound of claim 1, wherein the compound is propane-1-sulfonic acid {2,4-difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-amide having the structure:



or a pharmaceutically acceptable salt thereof.

56. A composition comprising: a pharmaceutically acceptable carrier; and a compound according to any one of Claims 1-55.

57. A kit comprising a compound according to any one of Claims 1-55 or a composition according to Claim 56.

58. A compound according to any one of Claims 1-55 for use as a medicament.

59. Use of a compound according to any one of Claims 1-55 or a composition according to Claim 56 in the preparation of a medicament for the treatment of a disease or condition for which modulation of Raf protein kinase activity provides a therapeutic benefit, wherein said Raf protein kinase is selected from the group consisting of B-Raf, any mutation of B-Raf, c-Raf-1, and any mutation of c-Raf-1.

60. The use according to Claim 59, wherein said disease or condition is selected from the group consisting of melanoma, glioma, thyroid cancer, liver cancer, lung cancer, colon cancer, cancer, acute pain, chronic pain, and polycystic kidney disease.

61. Use of a compound according to any one of Claims 1, 5, 6, 10, 11, 14-19 or 43-55 in the preparation of a pharmaceutical for the treatment of melanoma.

62. Use of a compound according to any one of Claims 1, 5, 6, 10, 11, 14-19 or 43-55 in the preparation of a pharmaceutical for the treatment of thyroid cancer.

63. Use of a compound according to any one of Claims 1, 5, 6, 10, 11, 14-19 or 43-55 in the preparation of a pharmaceutical for the treatment of colorectal cancer.

64. Use of a compound according to any one of Claims 1, 5, 6, 10, 11, 14-19 or 43-55 in the preparation of a pharmaceutical for the treatment of lung cancer.

65. Use of a compound according to any one of Claims 1, 5, 6, 10, 11, 14-19 or 43-55 in the preparation of a pharmaceutical for the treatment of prostate cancer.

66. Use of a compound according to any one of Claims 1, 5, 6, 10, 11, 14-19 or 43-55 in the preparation of a pharmaceutical for the treatment of liver cancer.

67. Use of a compound according to any one of Claims 1, 5, 6, 10, 11, 14-19 or 43-55 in the preparation of a pharmaceutical for the treatment of glioma.

68. Use of a compound according to any one of Claims 20, 30, 34, 37, 38 or 40-42 in the preparation of a pharmaceutical for the treatment of polycystic kidney disease.

69. Use of a compound according to any one of Claims 20, 30, 34, 37, 38 or 40-42 in the preparation of a pharmaceutical for the treatment of acute pain.

70. Use of a compound according to any one of Claims 20, 30, 34, 37, 38 or 40-42 in the preparation of a pharmaceutical for the treatment of chronic pain.