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(71) Applicant(s)
UNIVERSITY OF ROCHESTER

(72) Inventor(s)
Gelbard, Harris A.;Dewhurst, Stephen;Goodfellow, Val S.;Wiemann, Torsten;Ravula, Satheesh Babu;Loweth, Colin J.

(74) Agent / Attorney
Griffith Hack, GPO Box 1285, Melbourne, VIC, 3001

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(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF ROCHESTER** [US/US]; Box OTT, 601 Elmwood Avenue, Rochester, New York 14642 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GELBARD, Harris, A.** [US/US]; Pittsford, New York (US). **DEWHURST, Stephen** [US/US]; Rochester, New York (US). **GOODFELLOW, Val, S.** [US/US]; Encinitas, California (US). **WIEMANN, Torsten** [DE/US]; Encinitas, California (US). **RAVULA, Satheesh, Babu** [US/US]; San Diego, California (US). **LOWETH, Colin, J.** [US/US]; San Marcos, California (US).

(74) Agent: **CURFMAN, Christopher L.**; McKeon, Meunier, Carlin & Curfman, LLC, Suite 900, 817 W. Peachtree Street NW, Atlanta, Georgia 30308 (US).

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(54) Title: BICYCLIC HETEROARYL KINASE INHIBITORS AND METHODS OF USE

(57) Abstract: Provided are compounds having an inhibitory effect on kinases including Mixed Lineage Kinases. Also provided are pharmaceutical compositions, methods of preparing the compounds, synthetic intermediates, and methods of using the compounds, independently or in combination with other therapeutic agents, for treating diseases and conditions that are affected by Mixed Lineage Kinase inhibition. Also provided are methods of treatment of neuropsychiatric disorders that comprise the inhibition of Mixed Lineage Kinases.

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BICYCLIC HETEROARYL KINASE INHIBITORS AND METHODS OF USE

ACKNOWLEDGMENT OF GOVERNMENT SUPPORT

[001] This invention was made with government support under MH064570 awarded by National Institutes of Health. The government has certain rights in the invention.

CROSS REFERENCE TO RELATED APPLICATIONS

[002] This application claims the benefit of priority to U.S. Provisional Application No. 61/347,694, filed May 24, 2010, which is incorporated by reference herein in its entirety.

BACKGROUND

[003] Mammalian protein kinases are involved in the regulation of important cellular functions. Due to the fact that dysfunctions in protein kinase activity have been associated with several diseases and disorders, protein kinases are targets for drug development.

[004] Mixed lineage kinases (MLKs) are MAPK kinase kinases that target JNK and p38 MAPK for activation in response to diverse stimuli that stress cells. As a result, the MLKs regulate a broad range of cellular processes. MLK3 is the most widely expressed MLK family member and is present in neurons and brain-resident mononuclear phagocytes. It is activated by GTPases of the Ras superfamily, such as Cdc42 and Rac, which trigger protein dimerization via a leucine zipper interface, resulting in auto-phosphorylation at Thr277 and Ser281 within the protein activation loop and subsequent activation of the enzyme.

[005] Preclinical studies of the mixed lineage kinase (MLK) inhibitor CEP1347 have shown that this agent can protect neurons against a considerable range of insults, including exposure to the Alzheimer's peptide, Aβ. Studies using the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinsonism have demonstrated the efficacy of CEP1347 in treating motor deficits and neuronal degeneration, and CEP1347-mediated neuroprotection has also been observed in an in vitro model for Parkinson's Disease, using methamphetamine-exposed human mesencephalic-derived neurons. This finding suggests that CEP1347 might also be protective in the context of neurologic complications such as HIV-associated dementia (HAD). In fact, Bodner *et al.* have shown that CEP1347 can protect primary rat hippocampal neurons as well as dorsal root ganglion neurons from the otherwise lethal effects of exposure to HIV-1 gp120. It has been determined that CEP1347 mediates this effect by inhibiting the activity of the mixed lineage kinase (MLK) family.

[006] Maggirwar *et al.* recently examined the effect of the HIV-1 neurotoxins Tat and gp120 on MLK3. Tat and gp120 were shown to induce autophosphorylation of MLK3 in

primary rat neurons and this was abolished by the addition of CEP1347. These studies suggest that the normal function of MLK3 is compromised by these HIV-1 neurotoxins, resulting in the downstream signaling events that result in neuronal death and monocyte activation (with release of inflammatory cytokines). Most recently, Eggert *et al.* have demonstrated that CEP1347 is neuroprotective in an in vivo model of HIV-1 infection, reversing microglial activation and restoring normal synaptic architecture, as well as restoring macrophage secretory profiles to a trophic vs. toxic phenotype in response to HIV-1 infection. Eggert, D., Gorantla, S., Poluekova, L., Dou, H., Schifitto, G., Maggirwar, S.B., Dewhurst, S., Gelbard, H.A. and H.E. Gendelman: "Neuroprotective Activities of CEP-1347 in Models of HIV-1 Encephalitis," *J. Immunol.* 2010 Jan 15;184(2):746-56. Epub 2009 Dec 4.]

[007] Recently, MLK3 has been shown to drive the production of the HIV virus. As a result, several lines of evidence now support that an inhibitor of MLK3 could serve as a treatment for numerous neurological conditions, including neuroAIDS. CEP1347 does not have ideal pharmacokinetic properties, which could potentially affect its ability to gain entry, or remain at therapeutic concentrations in the CNS. Other small molecule MLK3 inhibitors are needed that have improved pharmacokinetic and brain penetrating properties.

[008] An inhibitor of MLK3 could also find use in the treatment of psychological disorders. Depression is a complex disease that has a multifactorial etiology. This may include genetic factors, changes in normal neuronal signaling, and reduced levels of certain neurotrophins (such as brain-derived neurotrophic factor, BDNF) within particular regions of the brain (Krishnan, V., and E. J. Nestler. 2008. Nature 455:894-902). Treatments for depression include drugs such as SSRIs, as well as cognitive and behavioral therapy ("talk therapy") and other inventions such as exercise. Interestingly, SSRIs and exercise share the common property that they promote neurogenesis; this is thought to be related to their anti-depressive effects because of effects on neuronal plasticity and remodeling (Krishnan, supra).

[009] Pharmacologic blockade of mixed lineage kinase 3 (MLK3) has been shown to result in activation of neurotrophin-mediated signaling pathways, and increased expression of neurotrophin receptors - resulting in enhanced responsiveness to endogenous neurotrophins, including BDNF (Wang, L. H., A. J. Paden, and E. M. Johnson, Jr. 2005. J *Pharmacol Exp Ther* 312:1007-19). MLK3 inhibitors have also been shown to increase production of BDNF itself (Conforti, P. *et al.* 2008. *Mol Cell Neurosci* 39:1-7).

[010] Combined treatment with SSRIs and MLK3 inhibitors could result in the synergistic promotion of neurogenesis, due to the neurotrophin-sensitizing effects of MLK3 inhibitors and their ability to directly upregulate BDNF (Wang and Conforti, *supra*). Increase of the

therapeutic effectiveness of SSRIs (and possibly talk therapy and exercise also) could also result if the compounds were coadministered.

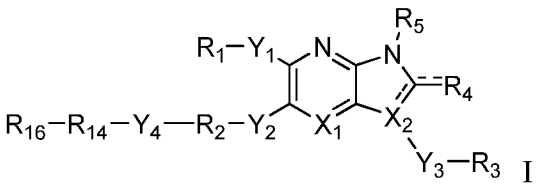
[011] Exposure to MLK3 inhibitors may also compensate for lowered BDNF levels in hippocampus of persons with depression, thereby alleviating depression (based on the "BDNF hypothesis") (Krishnan, *supra*).

[012] Dual leucine zipper kinase (DLK) is a member of the MLK family of kinases. Inhibiting MLKs can interrupt multiple signaling pathways related to glucotoxicity and reactive oxygen species. The etiology of diabetic neuropathy is associated with the activation of the JNK and p38 MAP kinase pathways. Members of the MLK family, including DLK, represent targets for the treatment of diseases including diabetic neuropathy, and specific inhibitors of MLK3, as well as mixed DLK/MLK3 inhibitors can be used to treat those diseases.

SUMMARY

[013] In accordance with the purposes of the disclosed materials, compounds, compositions, articles, devices, and methods, as embodied and broadly described herein, the disclosed subject matter releates to compositions and methods of making and using the compositions. In other aspect, disclosed herein are compounds having an inhibitory effect on kinases inclusing LRRK2, DLK, MLK1, MLK2, and MLK3. In a related aspect, also disclosed herein are compounds of Formula I as described below. Thus, provided herein are novel compounds that can be used for therapeutic methods involving modulation of kinases. Also provided are pharmaceutical compositions, methods of preparing the compounds, synthetic intermediates, and methods of using the compounds, independently or in combination with other therapeutic agents, for treating diseases and conditions affected by kinase inhibition.

[014] The present invention generally provides for compounds of Formula I:



I

wherein:

dashed lines indicate that a second bond may alternatively be present or absent, and are absent when X_2 is N;

X_1 is chosen from CH and N;

X_2 is chosen from CR_{13} and N;

Y_1 is $-(CR_{6a}R_{6b})_m$-Z_1-$(CR_{7a}R_{7b})_n-$;

Y_2 is $-(CR_{8a}R_{8b})_p$-Z_2-$(CR_{9a}R_{9b})_q-$;

Y_3 is $-(CR_{10a}R_{10b})_r$-Z_3-$(CR_{11a}R_{11b})_s-$;

Y_4 is $-(CH_2)_t$-Z_4-;

Z_1, Z_2, and Z_3, are each independently chosen from a bond, O, S, S(O), $S(O)_2$, $N(R_{12})$, C(O), $C(O)N(R_{12})$, $N(R_{12})C(O)$, $S(O)_2N(R_{12})$, and $N(R_{12})S(O)_2$;

Z_4 is chosen from a bond, O, and N;

m, n, p, q, r, and s are each independently an integer from 0 to 6;

t is an integer from 0 to 2;

R_1, R_2 , and R_3 are independently chosen from hydrogen, halo, lower alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, lower cycloalkyl, heterocycloalkyl, aryl, heteroaryl, acyl, amido, amino, alkoxy, hydroxy, cyano, and nitro, any of which may be optionally substituted; or R_1 and R_2 may each additionally be heteroalkyl, and may be joined together such that R_1 and R_2 together form an alkylene, alkenylene, or heteroalkyl bridge comprising from 3 to 5 atoms, which may be optionally substituted;

R_4 is chosen from hydrogen, (O), (S), halogen, hydroxy, cyano, nitro, lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, lower cycloalkyloxy, lower thioalkoxy, lower heterocycloalkyl, aryl, lower aralkyl, lower heteroaryl, lower heteroaralkyl, amido, acyl, amino, and lower alkoxy, any of which may be optionally substituted; or R_3 and R_4 may each additionally be heteroalkyl, and may be joined together such that R_1 and R_2 together form an alkylene, alkenylene, or heteroalkyl bridge comprising from 3 to 5 atoms, which may be optionally substituted;

R_5 and R_{13} are each independently chosen from hydrogen, halogen, hydroxy, cyano, nitro, lower alkyl, lower alkene, lower alkyne, lower aryl, lower arylalkyl, lower cycloalkyl, lower cycloalkylalkyl, lower heteroaryl, lower heteroarylalkyl, lower heterocycloalkyl, lower heterocycloalkylalkyl, and lower alkoxy, any of which may be optionally substituted; and additionally, R_{13} and R_3 may be joined together to form a lower spiro-cycloalkyl or spiro-phenyl comprising from 3 to 6 atoms, which may be optionally substituted; and if X_2 is N, then R_{13} is absent;

R_{6a}, R_{6b}, R_{7a}, R_{7b}, R_{8a}, R_{8b}, R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a}, R_{11b}, and R_{12} are each independently chosen from a bond, hydrogen, halogen, hydroxy, C_1-C_3 alkoxy and C_1-C_3 alkyl;

R_{14} is chosen from null, lower cycloalkyl, lower heterocycloalkyl, phenyl, and lower heteroaryl, any of which may be optionally substituted; and

R_{16} is chosen from lower alkyl, carboxyl, carbonyl, alkoxyethanone, carbamate, sulfonyl, heteroaryl, heteroarylalkyl, aryl, and arylalkyl.

[015] When, for example, Y_1 is $-(CR_{6a}R_{6b})_m$-Z_1-$(CR_{7a}R_{7b})_n-$, and m and n are both 0, and Z_1 is a bond, then Y_1 collapses to a direct bond linking the parent ring system with R_1. This applies to all similar constructions used herein, including Y_2 and Y_3. Also, when for example Y_1 is $-(CR_{6a}R_{6b})_m$-Z_1-$(CR_{7a}R_{7b})_n-$, the rightmost portion of Y_1 attaches to the parent molecule.

[016] In certain embodiments, Y_1, Y_2, Y_3, and Y_4 are no more than 6 atoms in length.

[017] In certain embodiments, R_4 is chosen from hydrogen, (O), and (S).

[018] In certain embodiments, R_4 is (O), the second bond linking R_4 and the fused bicyclic core is present, and the second bond in the five-membered portion of the fused bicyclic core is absent.

[019] In certain embodiments, R_4 is hydrogen, the second bond linking R_4 and the fused bicyclic core is absent, and the second bond in the five-membered portion of the fused bicyclic core is present.

[020] In certain embodiments, R_4 is chosen from hydrogen, halogen, lower alkyl, and deuterium.

[021] In certain embodiments,

X_1 is CH; and

X_2 is C.

[022] In certain embodiments,

X_1 is N; and

X_2 is N.

[023] In certain embodiments,

X_1 is CH; and

X_2 is N.

[024] In certain embodiments,

X_1 is N; and

X_2 is C.

[025] In certain embodiments,

m and n are both 0;

Z_1 is a bond; and

R_1 and R_5 are both hydrogen.

[026] In certain embodiments,

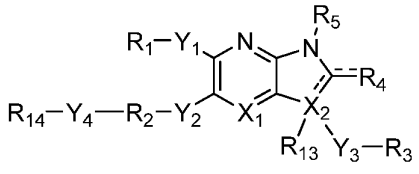
p and r are each independently an integer from 0 to 3;

q and s are each 0; and

Z_2 and Z_3 are each independently chosen from a bond and O.

[027] In certain embodiments, R_{6a}, R_{6b}, R_{7a}, R_{7b}, R_{8a}, R_{8b}, R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a}, R_{11b}, and R_{12} are all hydrogen.

[028] In certain embodiments, compounds have structural Formula II



II

wherein:

dashed lines indicate that a second bond may alternatively be present or absent;

X_1 is chosen from CH and N;

X_2 is chosen from C and N;

Y_1, Y_2, and Y_3 are independently chosen from a bond, lower alkyl, lower carboxyl, and lower heteroalkyl;

Y_4 is chosen from $–(CH_2)_m$, C(O), $–(CH_2)_mO–$, and $–(CH_2)_mN–$;

m is an integer from 0 to 2;

R_1, R_2, and R_3 are independently chosen from lower alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, lower cycloalkyl, heterocycloalkyl, aryl, heteroaryl, acyl, amido, amino, alkoxy, hydroxy, cyano, and nitro, any of which may be optionally substituted; or R_1 and R_2 may each additionally be heteroalkyl, and may be joined together such that R_1 and R_2 together form an alkylene, alkenylene, or heteroalkyl bridge comprising from 3 to 5 atoms, which may be optionally substituted;

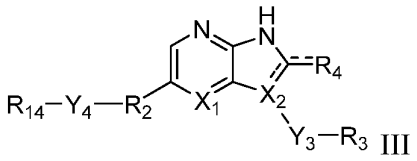
R_4 is chosen from hydrogen, (O), and (S);

R_5 is chosen from hydrogen, hydroxy, cyano, lower alkyl, lower cycloalkyl, and lower alkoxy, any of which may be optionally substituted;

R_{13} is chosen from hydrogen, halogen, hydroxy, cyano, nitro, lower alkyl, lower cycloalkyl, lower cycloalkylalkyl, and lower alkoxy, any of which may be optionally substituted; and additionally, R_{13} and R_3 may be joined together to form a lower spiro-cycloalkyl or spiro-phenyl comprising from 3 to 6 atoms, which may be optionally substituted; and

R_{14} is chosen from null, lower cycloalkyl, lower heterocycloalkyl, phenyl, and lower heteroaryl, any of which may be optionally substituted.

[029] In certain embodiments, compounds have structural Formula III



III

wherein:

dashed lines indicate that a second bond may alternatively be present or absent;

X_1 and X_2 are independently chosen from CH and N;

Y_3 is chosen from a bond, lower alkyl, lower carboxyl, and lower heteroalkyl;

Y_4 is chosen from O, S, C(O), SO, SO_2, NH, $N(CH_3)$, CH_2, CHF, CF_2, $CH(CH_3)$, $C(CH_3)_2$, CH_2O–, and –CH_2N–; –$(CH_2)_m$–, –$(CH_2)_mO$–, and –$(CH_2)_mN$–;

m is an integer from 0 to 1;

R_2 is chosen from phenyl and 6-membered monocyclic heteroaryl, either of which is optionally substituted with one or more substituents chosen from deuterium, halogen, hydroxy, lower amino, lower amido, C_1-C_3 alkoxy, and C_1-C_3 alkyl;

R_3 is cycloalkyl, aryl, heteroaryl, bicyclic heteroaryl, any of which is optionally substituted with one or more substituents chosen from deuterium, halogen, hydroxy, lower amino, lower amido, lower carboxyl, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), cyano, haloalkyl, phenyl, cycloalkyl, heteroaryl, and cycloheteroalkyl;

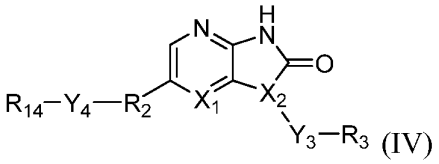
R_4 is chosen from hydrogen, CH_3, (O), and (S); and

R_{14} is chosen from lower heteroalkyl, lower heterocycloalkyl, and lower heteroaryl, any of which is optionally substituted with one or more substituents chosen from deuterium, halogen, hydroxy, lower amino, lower amido, lower carboxyl, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), haloalkyl, phenyl, benzyl, and lower cycloalkyl.

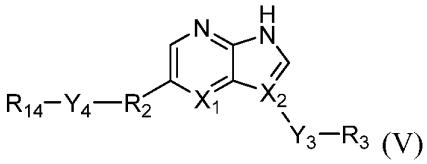
[030] In certain embodiments, compounds wherein X_1 is N, X_2 is N, or both X_1 and X_2 are N.

[031] The compound any of the preceding claims, wherein R_4 is CH_3

[032] In certain embodiments, compounds have a structural Formula chosen from Formula IV and Formula V:



(IV)



(V)

wherein:

X_1 and X_2 are independently chosen from CH and N;

Y_3 is chosen from a bond, lower alkyl, lower carboxyl, and lower heteroalkyl;

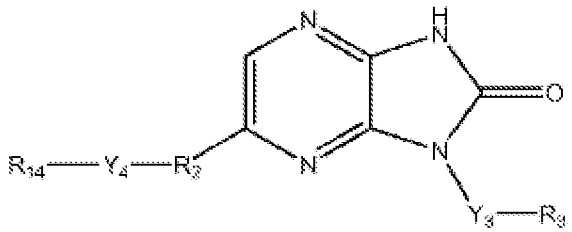
Y_4 is chosen from C(O), $-(CH_2)_m-$, $-(CH_2)_mO-$, and $-(CH_2)_mN-$;

m is an integer from 0 to 1;

R_2 and R_3 are independently chosen from lower cycloalkyl, lower heterocycloalkyl, lower aryl, and lower heteroaryl, any of which may be optionally substituted; and

R_{14} is chosen from null, lower cycloalkyl, lower heterocycloalkyl, phenyl, and lower heteroaryl, any of which may be optionally substituted.

[032A] In one aspect, the present invention provides a compound of structural Formula VI



(VI)

or a salt thereof, wherein:

Y_3 is chosen from a bond, lower alkyl, lower carboxyl, and lower heteroalkyl;

Y_4 is chosen from O, S, C(O), SO, SO_2, NH, $N(CH_3)$, CH_2, CHF, CF_2, $CH(CH_3)$, $C(CH_3)_2$, CH_2O—, and —CH_2N—; and

R_2 is chosen from phenyl and 6-membered monocyclic heteroaryl, either of which is optionally substituted with one or more substituents chosen from deuterium, halogen, hydroxy, lower amino, lower amido, C_1-C_3 alkoxy, and C_1-C_3 alkyl;

R_3 is chosen from cycloalkyl, aryl, heteroaryl, bicyclic heteroaryl, any of which is optionally substituted with one or more substituents chosen from deuterium, halogen, hydroxy, lower amino, lower amido, lower carboxyl, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), cyano, haloalkyl, phenyl, cycloalkyl, heteroaryl, and cycloheteroalkyl;

R_{14} is chosen from lower heteroalkyl, lower heterocycloalkyl, and lower heteroaryl, any of which is optionally substituted with one or more substituents chosen from deuterium, halogen, hydroxy, lower amino, lower amido, lower carboxyl, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), haloalkyl, phenyl, benzyl, and lower cycloalkyl.

[033] In certain embodiements, R_2 is phenyl optionally substituted with one or more substituents chosen from halogen, hydroxy, lower amino, lower amido, C_1-C_3 alkoxy, and C_1-C_3 alkyl.

[034] In certain embodiements, Y_3 is chosen from a bond or CH_2.

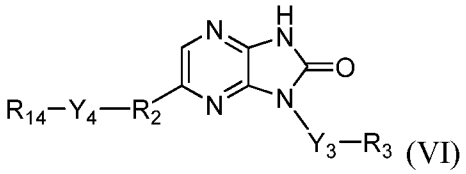
[035] In certain embodiements, R_3 is chosen from phenyl or 5/6-fused bicyclic heteroaryl, either of which is optionally substituted with one or more substitutents chosen from halogen, hydroxy, cyano, lower amino, lower amido, lower phenylamido, lower phenylalkylamido, lower heterocycloalkyl, lowerheterocycloalkyl, loweralkylheterocycloalkyl, C_1-C_3 alkoxy, and C_1-C_3 alkyl.

[036] In certain embodiements, R_{14} is a monocyclic heterocycloalkyl optionally substituted with one or more substituents chosen from halogen, hydroxy, lower amino, lower amido, lower carboxyl, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), haloalkyl, phenyl, benzyl, and lower cycloalkyl.

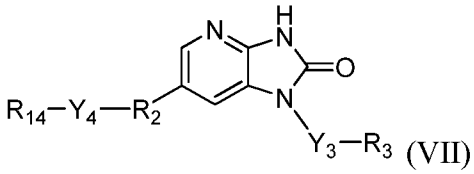
[037] In certain embodiements, Y_4 is chosen from O, S, C(O), NH, and CH_2,

[038] In certain embodiements, R_{14} is piperazinyl or morphilino, optionally substituted with one or more substituents chosen from halogen, hydroxy, lower amino, lower amido, lower carboxyl, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), haloalkyl, phenyl, benzyl, and lower cycloalkyl.

[039] In certain embodiments, compounds have a structural Formula chosen from Formula VI, Formula VII, Formula VIII, and Formula IX:



(VI)



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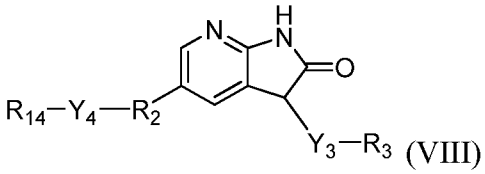

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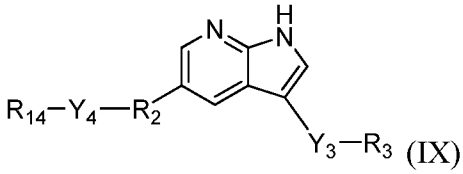


(IX)

wherein

Y_3 is chosen from a bond, lower alkyl, lower carboxyl, and lower heteroalkyl;

Y_4 is chosen from C(O), $–(CH_2)_m–$, $–(CH_2)_mO–$, and $–(CH_2)_mN–$;

m is an integer from 0 to 1;

R_2 is chosen from phenyl, 6-membered monocyclic heteroaryl, and 5/6-fused bicyclic heteroaryl, any of which may be optionally substituted;

R_3 is chosen from lower cycloalkyl, phenyl, and lower heteroaryl, any of which may be optionally substituted;

R_{14} is chosen from null, lower cycloalkyl, lower heterocycloalkyl, phenyl, and lower heteroaryl, any of which may be optionally substituted.

[040] In certain embodiments, R_2 and R_3 are each independently chosen from lower cycloalkyl, lower aryl, and monocyclic or bicyclic heteroaryl, any of which may be optionally substituted.

[041] In certain embodiments, R_2 is substituted with one or more substituents chosen from halogen, hydroxy, lower amino, C_1-C_3 alkoxy and C_1-C_3 alkyl.

[042] In further embodiments, R_2 is chosen from phenyl and lower heteroaryl, any of which may be optionally substituted.

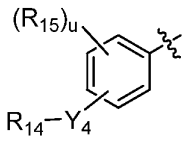
[043] In further embodiments, R_2 is chosen from phenyl, 6-membered monocyclic heteroaryl, and 5/6-fused bicyclic heteroaryl, any of which may be optionally substituted.

[044] In further embodiments, R_2 is chosen from phenyl, pyridinyl, pyrimidinyl, and indolyl, any of which may be optionally substituted.

[045] In further embodiments, R_2 is substituted with one or more substituents chosen from fluorine, hydroxy, NH_2, $NH(CH_3)$, $N(CH_3)_2$, methoxy, and methyl.

[046] In further embodiments, R_2 is optionally substituted phenyl.

[047] In further embodiments, R_2 is chosen from



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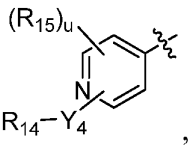

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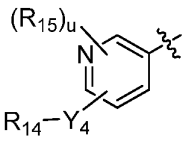

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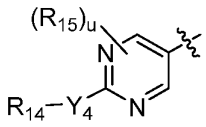

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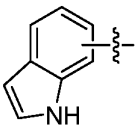


,

wherein

u is an integer from 0 to 3;

Y_4 is chosen from O, S, C(O), SO, SO_2, NH, $N(CH_3)$, CH_2, CHF, CF_2, $CH(CH_3)$, $C(CH_3)_2$, CH_2O–, and –CH_2N–; –$(CH_2)_m$–, –$(CH_2)_mO$–, and –$(CH_2)_mN$–;

m is an integer from 0 to 1;

R_{14} is chosen from null, lower cycloalkyl, lower heterocycloalkyl, phenyl, and lower heteroaryl, any of which may be optionally substituted; and

each R_{15} is independently chosen from halogen, hydroxy, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, lower amino, lower amido, lower sulfonamido, and lower sulfonyl.

[048] In certain embodiments, R_{14} is chosen from piperazinyl, morpholinyl, pyrrolyl, and $N(CH_3)_2$.

[049] In certain embodiments, each R_{15} is independently chosen from R_{15} is independently chosen from fluorine, hydroxy, NH_2, $NH(CH_3)$, $N(CH_3)_2$, $NS(O)_2CH_3$, methoxy, and methyl.

[050] In certain embodiments,

Y_4 is $-(CH_2)_m-$;

m is 0;

R_{14} is null;

u is an integer from 0 to 3; and

R_{15} is independently chosen from R_{15} is independently chosen from fluorine, hydroxy, NH_2, $NH(CH_3)$, $N(CH_3)_2$, $NS(O)_2CH_3$, methoxy, and methyl.

[051] In certain embodiments, Y_4 is chosen from C(O), O, N, and $-CH_2-$.

[052] In certain embodiments, Y_4 is $-CH_2-$.

[053] In certain embodiments, Y_3 is chosen from a bond and lower alkyl.

[054] In certain embodiments, Y_3 is chosen from a bond and methyl.

[055] In certain embodiments, Y_3 is a bond.

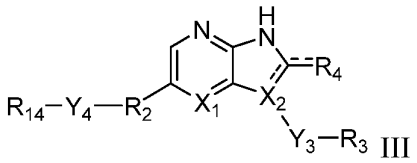
[056] In certain embodiments, R_3 is chosen from lower cycloalkyl, lower aryl, and monocyclic or bicyclic heteroaryl, any of which may be optionally substituted.

[057] In certain embodiments, R_3 is substituted with one or more substituents chosen from halogen, hydroxy, lower amino, lower amido, lower phenylamido, lower phenylalkylamido, lower heterocycloalkyl, lowerheterocycloalkyl, loweralkylheterocycloalkyl, C_1-C_3 alkoxy and C_1-C_3 alkyl.

[058] In certain embodiments, R_3 is chosen from benzothiazolyl, pyrrolopyridinyl, indanyl, cyclopropyl, cyclopentyl, phenyl, pyridinyl, pyrimidinyl, and indolyl, any of which may be optionally substituted.

[059] In certain embodiments, R_3 is substituted with one or more substituents chosen from fluorine, chlorine, hydroxy, NH_2, $NH(CH_3)$, $N(CH_3)_2$, $C(O)NH_2$, $C(O)NHCH_3$, morpholino, piperazinyl, methylpiperazinyl, acetamido, methylacetamido, methylpropionamido, phenylacetamidomethylene, benzamidomethylene, phenylpropanamidomethylene, methoxy and methyl.

[060] In certain embodiments are provided a compound of structural Formula III



III

or a salt thereof, wherein:

dashed lines indicate that a second bond may alternatively be present or absent;

X_1 and X_2 are independently chosen from CH and N;

Y_3 is a bond;

Y_4 is chosen from O, S, C(O), SO, SO_2, NH, $N(CH_3)$, CH_2, CHF, CF_2, $CH(CH_3)$, $C(CH_3)_2$, CH_2O–, and –CH_2N–; –$(CH_2)_m$–, –$(CH_2)_mO$–, and –$(CH_2)_mN$–;

m is an integer from 0 to 1;

R_2 is chosen from phenyl and 6-membered monocyclic heteroaryl, either of which may be optionally substituted;

R_3 is optionally substituted bicyclic heteroaryl;

R_4 is chosen from hydrogen, CH_3, (O), and (S);

R_{14} is optionally substituted monocyclic heterocycloalkyl.

[061] In certain embodiments, R_3 is an optionally substituted 5/6-fused bicyclic heteroaryl.

[062] In certain embodiments, wherein Y_4 is CH_2.

[063] In certain embodiments, R_{14} is optionally substituted piperazinyl.

[064] In certain embodiments, R_2 is chosen from hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_3-C_{10} cycloalkyl, C_1-C_4 alkyloxy, C_3-C_{10} cycloalkyloxy, aryl, cyano or nitro.

[065] In certain embodiments, R_1 and R_2 together form a butadienylene bridge.

[066] In certain embodiments,

m and n are both 0;

Z_1 is a bond;

R_1, R_5, and R_4 are hydrogen; and

R_2 and R_3 are each independently chosen from aryl and heteroaryl, either of which may be optionally substituted.

[067] In certain embodiments,

m and n are both 0;

Z_1 is a bond;

R_1, R_5, and R_4 are hydrogen;

R_2 is selected from the group consisting of aryl and heteroaryl, either of which may be optionally substituted; and

R_3 is chosen from 5-subsituted-1*H*-indole, 5-substituted pyridine-2-amine, and 5-substituted pyrimidine-2-amine.

[068] In certain embodiments,

m is 0 or 1

n is 0;

Z_1 is a bond;

R_1, R_5, and R_4 are hydrogen; and

R_1 is chosen from 5-subsituted-1*H*-indole, 5-substituted pyridine-2-amine, and 5-substituted pyrimidine-2-amine; and

R_2 is chosen from 5-substituted-1,2,3-trimethoxybenzene, 4-substituted-1,2-dimethoxyphenyl, 5-substituted pyridine-2-amine, and 5-substituted pyrimidine-2-amine.

[069] In certain embodiments,

R_1, R_5, and R_4 are hydrogen; and

R_2 and R_3 are each independently chosen from aryl and heteroaryl, either of which may be optionally substituted.

[070] In certain embodiments of Formula I,

m and n are both 0;

Z_1 is a bond;

R_1, R_5, and R_4 are hydrogen,

R_2 is chosen from aryl and heteroaryl, either of which may be optionally substituted; and

R_3 is chosen from 5-subsituted-1*H*-indole, 5-substituted pyridine-2-amine, and 5-substituted pyrimidine-2-amine, any of which may be optionally substituted.

[071] In certain embodiments of Formula I,

m and n are both 0;

Z_1 is a bond;

R_1, R_5, and R_4 represent hydrogen,

R_3 is chosen from 5-subsituted-1*H*-indole, 5-substituted pyridine-2-amine, and 5-substituted pyrimidine-2-amine; and

R_2 is chosen from 5-substituted-1,2,3-trimethoxybenzene, 4-substituted-1,2-dimethoxybenzene, 5-substituted pyridine-2-amine, and 5-substituted pyrimidine-2-amine.

[072] In certain embodiments,

R_4 is (O), the second bond linking R_4 and the fused bicyclic core is present, and the second bond in the five-membered portion of the fused bicyclic core is absent;

m and n are both 0;

Z_1 is a bond;

R_1 and R_5 are each hydrogen; and

R_2 and R_3 are each independently chosen from aryl and heteroaryl, either of which may be optionally substituted.

[073] In certain embodiments,

R_4 is (O), the second bond linking R_4 and the fused bicyclic core is present, and the second bond in the five-membered portion of the fused bicyclic core is absent;

m and n are both 0;

Z_1 is a bond;

R_1 and R_5 are each hydrogen; and

R_2 is chosen from aryl and heteroaryl, either of which may be optionally substituted; and

R_3 is chosen from 5-subsituted-1*H*-indole, 5-substituted pyridine-2-amine, and 5-substituted pyrimidine-2-amine.

[074] In certain embodiments,

R_4 is (O), the second bond linking R_4 and the fused bicyclic core is present, and the second bond in the five-membered portion of the fused bicyclic core is absent;

m and n are both 0;

Z_1 is a bond;

R_1 and R_5 are each hydrogen;

R_3 is chosen from 5-subsituted-1*H*-indole, 5-substituted pyridine-2-amine, or 5-substituted pyrimidine-2-amine; and

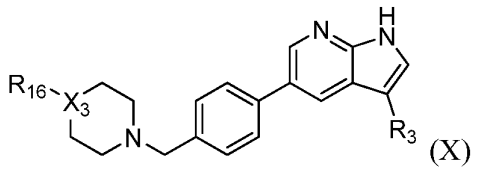
R_2 is chosen from 5-substituted-1,2,3-trimethoxybenzene, 4-substituted-1,2-dimethoxybenzene, 5-substituted pyridine-2-amine, and 5-substituted pyrimidine-2-amine.

[075] In certain embodiments, optionally substituted groups are substituted with one or more substituent chosen from halogen, hydroxy, C_1-C_3 alkoxy and C_1-C_3 alkyl.

[076] In certain embodiments, R_4 is mono- or poly-substituted with fluorine.

[077] In certain embodiments, R_5 is mono- or poly-substituted with fluorine.

[078] In certain embodiments, compounds have structural Formula X:



(X)

wherein

X_3 is chosen from CH, N, and O;

R_3 is chosen from lower cycloalkyl, phenyl, and lower heteroaryl, any of which is optionally substituted with one or more substituents chosen from halogen, hydroxy, lower amino, lower amido, lower carboxyl, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), cyano, haloalkyl, phenyl, cycloalkyl, heteroaryl, and cycloheteroalkyl;

R_{16} is chosen from lower alkyl, lower carboxyl, carbonyl, alkoxyethanone, carbamate, sulfonyl, heteroaryl, heteroarylalkyl, aryl, arylalkyl, and heterocycloalkylcarbonyl, any of which may be optionally substituted, and when X_3 is O, R_{16} is null,

and wherein the compound of Formula X is optionally substituted at a carbon atom with one or more substituents chosen from deuterium, halogen, lower alkyl, lower haloalkyl, and lower haloalkoxy.

[079] In certain embodiments, the compound of Formula X is optionally substituted at a carbon atom with one or more substituents chosen from deuterium, halogen, lower alkyl, lower haloalkyl, and lower haloalkoxy.

[080] In certain embodiments, the compound of Formula X is optionally substituted at a carbon atom with one or more substituents chosen from deuterium, halogen, and lower alkyl.

[081] In certain embodiments, the compound of Formula X is substituted at a carbon atom with one or more substituents chosen from deuterium, fluorine, and methyl.

[082] In certain embodiments, X_3 is N.

[083] In certain embodiments, R_3 is chosen from benzothiazolyl, pyrrolopyridinyl, indanyl, cyclopropyl, cyclopentyl, phenyl, pyridinyl, pyrimidinyl, and indolyl, any of which is optionally substituted with one or more substituents chosen from fluorine, chlorine, hydroxy, NH_2, $NH(CH_3)$, $N(CH_3)_2$, $C(O)NH_2$, $C(O)NHCH_3$, morpholino, piperazinyl, methylpiperazinyl, acetamido, methylacetamido, methylpropionamido, phenylacetamidomethylene, benzamidomethylene, phenylpropanamidomethylene, methoxy, and methyl.

[084] In certain embodiments, R_3 is phenyl optionally substituted with one or more substiruents chosen from hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lowerhaloalkoxy, halogen, lower amino, lower carboxyl, and cyano.

[085] In certain embodiments, R_3 is heteroaryl.

[086] In certain embodiments, R_3 is optionally substituted bicyclic heteroaryl.

[087] In certain embodiments, R_3 is chosen from indanyl, indolyl, indazolyl, indolinonyl, benzothiophenyl, quinolinyl, isoquinolinyl, pyrrolopyrazinyl, and pyrrolopyridinyl, any of which is optionally substituted with one or more substituents chosen from hydroxy, lower alkyl, lower alkoxy, lower haloalkyl, lowerhaloalkoxy, halogen, lower amino, and lower carboxyl.

[088] In certain embodiments, R_3 is optionally substituted at a carbon atom with one or more substituents chosen from deuterium, halogen, and lower alkyl.

[089] In certain embodiments, R_3 is indanyl optionally substituted at a carbon atom with one or more substituents chosen from deuterium, halogen, and lower alkyl.

[090] In certain embodiments, R_{16} is lower alkyl.

[091] In certain embodiments R_2, R_3, or R_{14} is substituted with deuterium, fluorine, or methyl.

[092] In certain embodiments X_3 is N.

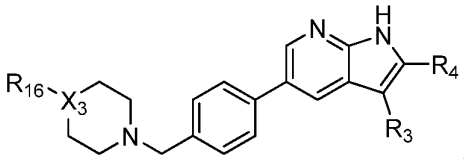
[093] In certain embodiments X_3 is N and R_{16} is CH_3.

[094] In certain embodiments, the compound of Formula X is substituted at a carbon atom on the pyrrolopyridinyl core with one or more substituents chosen from deuterium, fluorine, and methyl.

[095] In certain embodiments, the compound of Formula X is substituted at the 2-position on the pyrrolopyridinyl core with one or more substituents chosen from deuterium, fluorine, and methyl.

[096] In certain embodiments R_3 is indanyl or phenyl optionally substituted with with one or more substituents chosen from hydroxy, lower alkyl, lower alkoxy, lower haloalkyl, lowerhaloalkoxy, halogen, lower amino, and lower carboxyl.

[097] In certain embodiments, compounds have Structural Formual XI, wherein:



XI

X_3 is chosen from C, N, and O;

R_3 is chosen from lower cycloalkyl, phenyl, and lower heteroaryl, any of which may be optionally substituted;

R_4 is chosen from hydrogen, halogen, lower alkyl, and deuterium; and

R_{16} is chosen from lower alkyl, carboxyl, carbonyl, alkoxyethanone, carbamate, sulfonyl, heteroaryl, heteroarylalkyl, aryl, arylalkyl, and heterocycloalkylcarbonyl, any of which may be optionally substituted, and when X_3 is O, R_{16} is null.

[098] In certain embodiments is provided a compound chosen from Examples 1 to 279.

[099] Also provided herein is a compound as disclosed herein for use as a medicament.

[0100] Also provided herein is a compound as disclosed herein for use as a medicament for the treatment of an MLK-mediated disease.

[0101] Also provided herein is the use of a compound as disclosed herein in the manufacture of a medicament for the treatment of an MLK-mediated disease.

[0102] Also provided herein is a compound as disclosed herein for use as a medicament for the treatment of an LRRK2-mediated disease.

[0103] Also provided herein is the use of a compound as disclosed herein in the manufacture of a medicament for the treatment of an LRRK2-mediated disease.

[0104] Also provided herein is a pharmaceutical composition comprising a compound of Formula I or VI together with a pharmaceutically acceptable carrier.

[0105] Also provided is a pharmaceutical composition comprising a compound chosen from Examples 1 to 167 and 180-219.

[0106] Also provided herein is a method of inhibition of MLK comprising contacting MLK with a compound of Formula I or VI.

[0107] In certain embodiments, said MLK is MLK3.

[0108] In certain embodiments, said MLK is DLK.

[0109] In certain embodiments, said inhibition is selective over other kinases.

[0110] Also provided herein is a method of treatment of a MLK-mediated disease comprising the administration of a therapeutically effective amount of a compound of Formula I or VI to a patient in need thereof.

[0111] In certain embodiments, said disease is an inflammatory disease or a metabolic disease.

[0112] In certain embodiments, said disease is chosen from diabetes mellitus, hyperglycemia, retinopathy, nephropathy, neuropathy, ulcers, micro- and macroangiopathies, gout and diabetic foot disease, insulin resistance, metabolic syndrome, hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, peripheral inflammation, and HIV dementia.

[0113] Also provided herein is a method of treatment of a MLK-mediated disease comprising the administration of:

a) a therapeutically effective amount of a compound of Formula I or VI; and

b) another therapeutic agent.

[0114] In certain embodiments, said disorder a psychological disorder.

[0115] In certain embodiments, said disease is chosen from depression, bipolar disorder, and post-traumatic stress disorder (PTSD).

[0116] In certain embodiments, said disorder is a traumatic brain injury.

[0117] In certain embodiments, said traumatic brain injury is stroke.

[0118] In certain embodiments, said disorder is chosen from Alzheimer's Disease (AD), Parkinson's Disease, HIV dementia and HIV associated neurocognitive disorder (HAND).

[0119] In certain embodiments, said disorder is a neurologic disorder of hearing or vision.

[0120] In certain embodiments, said disorder is chosen from ototoxicity, hearing loss, acute injury to the inner ear, acoustic trauma, and injury resulting from blast noise.

[0121] In certain embodiments the methods of treatment disclosed herein additionally comprise the administration of a second therapeutic agent, as part of a therapeutic regimen. The compounds may be delivered in the same dosage form or separately, and further may be taken concurrently or one subsequent to the other.

[0122] In certain embodiments, said second therapeutic agent is a selective serotonin reuptake inhibitor (SSRI).

[0123] In certain embodiments, said second therapeutic agent is CEP1347.

[0124] Also provided herein is a method of treatment of a MLK-mediated disease comprising the administration of:

a) a therapeutically effective amount of a an MLK inhibitor; and

b) another therapeutic agent.

[0125] In certain embodiments, said second therapeutic agent is a selective serotonin reuptake inhibitor (SSRI).

[0126] In certain embodiments, said second therapeutic agent is CEP1347.

[0127] Also provided herein is a method of achieving an effect in a patient comprising the administration of a therapeutically effective amount of a compound as disclosed herein to a patient, wherein the effect is chosen from:

increased survival of cells of the nervous system, cochlear cells, vestibular cells or retinal cells;

increased survival of heart cells;

promotion of neurogenesis;

promotion of synaptogenesis;

prevention or reduction of neuronal damage;

restoration or improvement of neuronal function, including synaptic function;

suppression of neuroinflammation or peripheral inflammation;

suppression of activation of immune cells;

suppression of proliferation of hepatocytes following injury; and

suppression of proliferation of cancer cells.

[0128] In certain embodiments, the effect is chosen from:

increased survival of heart cells;

suppression of neuroinflammation or peripheral inflammation;

suppression of activation of immune cells;

suppression of proliferation of hepatocytes following injury; and

suppression of proliferation of cancer cells.

[0129] In certain embodiments, said immune cells are chosen from monocytes, macrophages and microglia.

[0130] In certain embodiments, the effect is chosen from:

increased survival of cells of the nervous system, cochlear cells, vestibular cells or retinal cells;

increased survival of heart cells;

promotion of neurogenesis;

promotion of synaptogenesis;

prevention or reduction of neuronal damage;

restoration or improvement of neuronal function, including synaptic function;

suppression of neuroinflammation or peripheral inflammation;

suppression of activation of immune cells;

suppression of proliferation of hepatocytes following injury; and

suppression of proliferation of cancer cells.

[0131] In certain embodiments, said immune cells are chosen from monocytes, macrophages and microglia.

[0132] In certain embodiments, the effect is chosen from:

increased survival of cells of the nervous system, cochlear cells, vestibular cells or retinal cells;

promotion of neurogenesis;

promotion of synaptogenesis;

prevention or reduction of neuronal damage; and

restoration or improvement of neuronal function.

[0133] Also provided herein is a method of treatment of a LKKR2-mediated disease comprising the administration of a therapeutically effective amount of a compound of Formula I or VI to a patient in need thereof.

[0134] In certain embodiments, said disease is a condition associated with neurodegeneration of dopaminergic pathways.

[0135] In certain embodiments, said condition associated with neurodegeneration of dopaminergic pathways is Parkinson's Disease.

[0136] Additional advantages of the disclosed subject matter will be set forth in part in the description that follows, and in part will be obvious from the description, or can be learned by practice of the aspects described below. The advantages described below will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive.

DETAILED DESCRIPTION

[0137] The compounds, compositions, articles, devices, and methods described herein may be understood more readily by reference to the following detailed description of specific aspects of the disclosed subject matter and the Examples.

[0138] Before the presentcompounds, compositions, articles, devices, and methods are disclosed and described it is to be understood that the aspects described below are not limited to specific synthetic methods or specific reagents, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting.

[0139] Also, throughout this specification, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which the disclosed matter pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

[0140] In this specification and in the claims that follow, reference will be made to a number of terms, which shall be defined to have the following meanings:

[0141] As used in the description and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example,

reference to "a composition" includes mixtures of two or more such compositions, reference to "the compound" includes mixtures of two or more such compounds, and the like.

[0142] "Optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

[0143] When ranges of values are disclosed, and the notation "from n_1 … to n_2" is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range "from 2 to 6 carbons" is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range "from 1 to 3 μM (micromolar)," which is intended to include 1 μM, 3 μM, and everything in between to any number of significant figures (*e.g.*, 1.255 μM, 2.1 μM, 2.9999 μM, etc.).

[0144] The term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[0145] The term "acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(O)CH_3$ group. An "alkylcarbonyl" or "alkanoyl" group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

[0146] The term "alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term "alkenylene" refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(–CH=CH–),(–C::C–)]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-propenyl, 2-methylpropenyl, butenyl, isobutenyl, 1,4-butadienyl, isoprenyl, vinyl, and the like. Unless otherwise specified, the term "alkenyl" may include "alkenylene" groups.

[0147] The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[0148] The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms. In certain embodiments, said alkyl will comprise from 1 to 10 carbon atoms. In further embodiments, said alkyl will comprise from 1 to 6 carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene (–CH_2–). Unless otherwise specified, the term "alkyl" may include "alkylene" groups.

[0149] The term "alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

[0150] The term "alkylidene," as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

[0151] The term "alkylthio," as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as defined above and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

[0152] The term "alkynyl," as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkynyl comprises from 2 to 6 carbon atoms. In further embodiments, said alkynyl comprises from 2 to 4 carbon atoms. The term "alkynylene" refers to a carbon-carbon triple bond attached at two positions such as ethynylene (–C:::C–, –C≡C–). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, 3-methylbutyn-1-yl, hexyn-2-yl, and the like. Unless otherwise specified, the term "alkynyl" may include "alkynylene" groups.

[0153] The terms "amido" and "carbamoyl," as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or vice versa. The term "C-amido" as used herein, alone or in combination, refers to a -C(O)N(RR') group with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated. The term "N-amido" as used herein, alone or in combination, refers to a RC(O)N(R')- group, with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated. The term "acylamino" as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an "acylamino" group is acetylamino ($CH_3C(O)NH$–).

[0154] The term "amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently chosen from hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. Additionally, R and R' may combine to form heterocycloalkyl, either of which may be optionally substituted.

[0155] The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such polycyclic ring systems are fused together. The term "aryl" embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl.

[0156] The term "arylalkenyl" or "aralkenyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

[0157] The term "arylalkoxy" or "aralkoxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[0158] The term "arylalkyl" or "aralkyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

[0159] The term "arylalkynyl" or "aralkynyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

[0160] The term "arylalkanoyl" or "aralkanoyl" or "aroyl,"as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, naphthoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, and the like.

[0161] The term aryloxy as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

[0162] The terms "benzo" and "benz," as used herein, alone or in combination, refer to the divalent radical C_6H_4= derived from benzene. Examples include benzothiophene and benzimidazole.

[0163] The term "carbamate," as used herein, alone or in combination, refers to an ester of carbamic acid (–NRC(O)O–) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein. The term "O-carbamyl" as used herein, alone or in combination, refers to a -OC(O)NRR' group; and the term "N-carbamyl" as used herein, alone or in combination, refers to a ROC(O)NR'- group. R and R' are as defined herein, or as defined by the specifically enumerated "R" groups designated.

[0164] The term "carbonyl," as used herein, when alone includes formyl [–C(O)H] and in combination is a –C(O)– group.

[0165] The term "carboxyl" or "carboxy," as used herein, refers to –C(O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-carboxy" group refers to a RC(O)O– group, where R is as defined herein. A "C-carboxy" group refers to a –C(O)OR groups where R is as defined herein.

[0166] The term "cyano," as used herein, alone or in combination, refers to –CN.

[0167] The term "cycloalkyl," or, alternatively, "carbocycle," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl group wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. In certain embodiments, said cycloalkyl will comprise from 5 to 7 carbon atoms. Examples of such cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, indanyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by, bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

[0168] The term "ester," as used herein, alone or in combination, refers to a carboxy group bridging two moieties linked at carbon atoms.

[0169] The term "ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

[0170] The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[0171] The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom. Haloalkoxy includes perhaloalkoxy. The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms. An example of perhaloalkoxy is perfluoromethoxy.

[0172] The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl, polyhaloalkyl, and perhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene (–CFH–), difluoromethylene ($–CF_2–$), chloromethylene (–CHCl–) and the like. The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms. Examples include perfluoromethyl.

[0173] The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms chosen from O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$.

[0174] The term "heteroaryl," as used herein, alone or in combination, refers to a 3 to 15 membered unsaturated heteromonocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which contains at least one atom chosen from O, S, and N. Additionally, a heteroaryl may contain one or two C(O), S(O), or $S(O)_2$ groups as ring members. In certain embodiments, said heteroaryl will comprise from 5 to

10 atoms. In certain embodiments, said heteroaryl will comprise from 5 to 7 atoms. In certain embodiments, said heteroaryl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heteroaryl will comprise from 1 to 2 heteroatoms as ring members. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, triazinyl, triazolyl, tetrazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[0175] The terms "heterocycloalkyl" and, interchangeably, "heterocycle," as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, wherein each said heteroatom may be independently chosen from N, O, and S. Additionally, a heterocycloalkyl may contain one or two C(O), S(O), or $S(O)_2$ groups as ring members. In certain embodiments, said hetercycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said hetercycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said hetercycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said hetercycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said hetercycloalkyl will comprise from 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycle groups include aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihy-dropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl,

tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

[0176] The term "hydrogen," as used herein, alone or in combination, may include deuterium.

[0177] The term "hydroxy," as used herein, alone or in combination, refers to –OH.

[0178] The term "lower," as used herein, alone or in a combination, where not otherwise specifically defined, means containing from 1 to and including 6 carbon atoms.

[0179] The term "lower alkyl," as used herein, alone or in a combination, means C_1-C_6 straight or branched chain alkyl. The term "lower alkenyl" means C_2-C_6 straight or branched chain alkenyl. The term "lower alkynyl" means C_2-C_6 straight or branched chain alkynyl.

[0180] The term "lower aryl," as used herein, alone or in combination, means phenyl or naphthyl, either of which may be optionally substituted as provided.

[0181] The term "lower heteroaryl," as used herein, alone or in combination, means either 1) monocyclic heteroaryl comprising five or six ring members, of which between one and four said members may be heteroatoms chosen from O, S, and N, or 2) bicyclic heteroaryl, wherein each of the fused rings comprises five or six ring members, comprising between them one to four heteroatoms chosen from O, S, and N.

[0182] The term "lower cycloalkyl," as used herein, alone or in combination, means a monocyclic cycloalkyl having between three and six ring members. Lower cycloalkyls may be unsaturated. Examples of lower cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0183] The term "lower heterocycloalkyl," as used herein, alone or in combination, means a monocyclic heterocycloalkyl having between three and six ring members, of which between one and four may be heteroatoms chosen from O, S, and N. Examples of lower heterocycloalkyls include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, and morpholinyl. Lower heterocycloalkyls may be unsaturated.

[0184] The term "lower carboxyl," as used herein, alone or in combination, means –C(O)R, wherein R is chosen from hydrogen, lower alkyl, cycloalkyl, cycloheterolkyl, and lower heteroalkyl, any of which may be optionally substituted with hydroxyl, (O), and halogen.

[0185] The term "lower amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently chosen from hydrogen, lower alkyl, and lower heteroalkyl, any of which may be optionally substituted. Additionally, the R and R' of a lower amino group

may combine to form a five- or six-membered heterocycloalkyl, either of which may be optionally substituted.

[0186] The term "nitro," as used herein, alone or in combination, refers to $–NO_2$.

[0187] The terms "oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

[0188] The term "oxo," as used herein, alone or in combination, refers to =O.

[0189] The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

[0190] The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[0191] The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer the $–SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

[0192] The term "N-sulfonamido" refers to a $RS(=O)_2NR'$- group with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated.

[0193] The term "S-sulfonamido" refers to a $-S(=O)_2NRR'$, group, with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated.

[0194] The terms "thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio. The term "sulfanyl," as used herein, alone or in combination, refers to –S–. The term "sulfinyl," as used herein, alone or in combination, refers to –S(O)–. The term "sulfonyl," as used herein, alone or in combination, refers to $–S(O)_2–$.

[0195] The term "thiol," as used herein, alone or in combination, refers to an –SH group.

[0196] The term "thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

[0197] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[0198] When a group is defined to be "null," what is meant is that said group is absent.

[0199] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include

acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

[0200] The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen or deuterium, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, lower haloalkylthio, lower perhaloalkylthio, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3, SH, SCH_3, $C(O)CH_3$, CO_2CH_3, CO_2H, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (*e.g.*, $-CH_2CH_3$), fully substituted (*e.g.*, $-CF_2CF_3$), monosubstituted (*e.g.*, $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (*e.g.*, $-CH_2CF_3$). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

[0201] The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety chosen from hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R^n where n=(1, 2, 3, …n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (*e.g.* aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. Thus, by way of example only, an unsymmetrical group such as –C(O)N(R)– may be attached to the parent moiety at either the carbon or the nitrogen.

[0202] Asymmetric centers exist in the compounds disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and 1-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Compounds can be prepared using diastereomers, enantiomers or racemic mixtures as starting materials. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Furthermore, diastereomer and enantiomer products can be separated by chromatography, fractional crystallization or other methods known to those of skill in the art. Additionally, the compounds disclosed herein may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Solvates, hydrates, isomorphs, polymorphs are also provided. Additionally, the compounds disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[0203] Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, *e.g.*, each enantiomer, diastereomer, and meso compound, and a mixture of isomers, such as a racemic or scalemic mixture.

[0204] The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position. When, for example, Y_1 is $-(CR_{6a}R_{6b})_m$-Z_1-$(CR_{7a}R_{7b})_n$-, and m and n are both 0, and Z_1 is a bond, then Y_1 collapses to a direct bond linking the parent ring system with R_1. This applies to all similar constructions used herein, including Y_2 and Y_3. Or, for example, when either of R_{6a} and R_{6b} of $(CR_{6a}R_{6b})_m$ are designated to be "a bond," and $m \geq 1$, then an additional bond forms between a C of $(CR_{6a}R_{6b})$ and an adjacent atom. When $m \geq 2$, then $(CR_{6a}R_{6b})_m$ may form an alkene (alkenylene) or alkyne (alkynylene).

[0205] By "reduce" or other forms of the word, such as "reducing" or "reduction," is meant lowering of an event or characteristic (*e.g.*, tumor growth). It is understood that this is typically in relation to some standard or expected value, in other words it is relative, but that it is not always necessary for the standard or relative value to be referred to. For example, "reduces tumor growth" means reducing the rate of growth of a tumor relative to a standard or a control.

[0206] By "prevent" or other forms of the word, such as "preventing" or "prevention," is meant to stop a particular event or characteristic, to stabilize or delay the development or progression of a particular event or characteristic, or to minimize the chances that a particular event or characteristic will occur. Prevent does not require comparison to a control as it is typically more absolute than, for example, reduce. As used herein, something could be reduced but not prevented, but something that is reduced could also be prevented. Likewise, something could be prevented but not reduced, but something that is prevented could also be reduced. It is understood that where reduce or prevent are used, unless specifically indicated otherwise, the use of the other word is also expressly disclosed.

[0207] By "treat" or other forms of the word, such as "treated" or "treatment," is meant to administer a composition or to perform a method in order to reduce, prevent, inhibit, or eliminate a particular characteristic or event (*e.g.*, tumor growth or survival). The term "control" is used synonymously with the term "treat."

[0208] As used herein, the terms "treating" and "treatment" refer to delaying the onset of, retarding or reversing the progress of, or alleviating or preventing either the disease or condition to which the term applies, or one or more symptoms of such disease or condition.

[0209] The term "patient" (and, equivalently, "subject") means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

[0210] The term "disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder," "syndrome," and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one or more of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and/or causes the human or animal to have a reduced duration or quality of life.

[0211] The term "neuropsychiatric disorder" includes, without limitation, psychological, psychiatric, and neurological disorders.

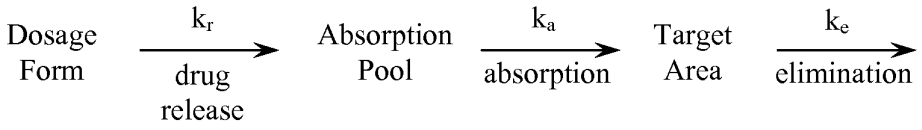
[0212] The term "HIV associated neurocognitive disorder (HAND)" is related to, and is intended to be substantially synonymous with, the terms HIV dementia, AIDS dementia, HIV encephalopathy, and NeuroAIDS.

[0213] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0214] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a subject. Administration is by any route including parenteral, and transmucosal (*e.g.*, oral, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, and the like.

[0215] As used herein, the term "prodrug" refers to a precursor compound that, following administration, releases the biologically active compound in vivo via some chemical or physiological process (*e.g.*, a prodrug on reaching physiological pH or through enzyme action is converted to the biologically active compound).

[0216] The terms "controlled release," "sustained release," "extended release," and "timed release" are intended to refer interchangeably to any drug-containing formulation in which release of the drug is not immediate, *i.e.*, with a "controlled release" formulation, oral administration does not result in immediate release of the drug into an absorption pool. The terms are used interchangeably with "nonimmediate release" as defined in *Remington: The Science and Practice of Pharmacy*, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2003). As discussed therein, immediate and nonimmediate release can be defined kinetically by reference to the following equation:



[0217] The "absorption pool" represents a solution of the drug administered at a particular absorption site, and k_r, k_a and k_e are first-order rate constants for (1) release of the drug from the formulation, (2) absorption, and (3) elimination, respectively. For immediate release dosage forms, the rate constant for drug release k_r is far greater than the absorption rate constant k_a. For controlled release formulations, the opposite is true, *i.e.*, $k_r << k_a$, such that the rate of release of drug from the dosage form is the rate-limiting step in the delivery of the drug to the target area.

[0218] The terms "sustained release" and "extended release" are used in their conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, for example, 12 hours or more, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period.

[0219] As used herein, the term "delayed release" refers to a pharmaceutical preparation that passes through the stomach intact and dissolves in the small intestine.

[0220] "MLK3 inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to MLK3 activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the MLK3 (assay name) described generally hereinbelow. "IC_{50}" is that concentration of inhibitor which reduces the activity and/or expression of an enzyme (*e.g.*, MLK

or MLK3) to half-maximal level. Certain compounds disclosed herein have been discovered to exhibit inhibition against MLK3. In certain embodiments, compounds will exhibit an IC50 with respect to MLK3 of no more than about 10 μM; in further embodiments, compounds will exhibit an IC_{50} with respect to MLK3 of no more than about 5 μM; in yet further embodiments, compounds will exhibit an IC_{50} with respect to MLK3 of not more than about 1 μM; in yet further embodiments, compounds will exhibit an IC_{50} with respect to MLK3 of not more than about 200 nM, as measured in the MLK3 assay described herein.

[0221] The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder. This amount will achieve the goal of reducing or eliminating the said disease or disorder.

[0222] The term "therapeutically acceptable" refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0223] The term "prodrug" refers to a compound that is made more active in vivo. Certain compounds disclosed herein may also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[0224] Prodrugs of compounds of Formula I are provided herein. Prodrugs of compounds provided herein include, but are not limited to, carboxylate esters, carbonate esters, hemi-esters, phosphorus esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo compounds,

or MLK3) to half-maximal level. Certain compounds disclosed herein have been discovered to exhibit inhibition against MLK3. In certain embodiments, compounds will exhibit an IC50 with respect to MLK3 of no more than about 10 μM; in further embodiments, compounds will exhibit an IC_{50} with respect to MLK3 of no more than about 5 μM; in yet further embodiments, compounds will exhibit an IC_{50} with respect to MLK3 of not more than about 1 μM; in yet further embodiments, compounds will exhibit an IC_{50} with respect to MLK3 of not more than about 200 nM, as measured in the MLK3 assay described herein.

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[0224] Prodrugs of compounds of Formula I or VI are provided herein. Prodrugs of compounds provided herein include, but are not limited to, carboxylate esters, carbonate esters, hemi-esters, phosphorus esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo compounds, phosphamides, glycosides, ethers, acetals, and ketals. Prodrug esters and carbonates may be formed, for example, by reacting one or more hydroxyl groups of compounds of Formula I, Formula II or

Formula VI with alkyl, alkoxy or aryl substituted acylating reagents using methods known to those of skill in the art to produce methyl carbonates, acetates, benzoates, pivalates and the like. Illustrative examples of prodrug esters of the compounds provided herein include, but are not limited to, compounds of Formula I or VI having a carboxyl moiety wherein the free hydrogen is replaced by C_1-C_4 alkyl, C_1-C_7 alkanoyloxymethyl, 1-((C_1-C_5)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_5)alkanoyloxy)-ethyl, C_1-C_5 alkoxycarbonyloxymethyl, 1-((C_1-C_5)alkoxycarbonyloxy)ethyl, 1-methyl-1-((C_1-C_5)alkoxycarbonyloxy)ethyl, N-((C_1-C_5)alkoxycarbonyl)aminomethyl, 1-(N-((C_1-C_5)alkoxycarbonyl)amino)ethyl, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (*e.g.*, beta-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl. Oligopeptide modifications and biodegradable polymer derivatives (as described, for example, in *Int. J. Pharm.* 115, 61-67, 1995) are within the scope of the present disclosure. Methods for selecting and preparing suitable prodrugs are provided, for example, in the following: T. Higuchi and V. Stella, "Prodrugs as Novel Delivery Systems," Vol. 14, ACS Symposium Series, 1975; H. Bundgaard, *Design of Prodrugs*, Elsevier, 1985; and *Bioreversible Carriers in Drug Design*, ed. Edward Roche, American Pharmaceutical Association and Pergamon Press, 1987.

[0225] The compounds disclosed herein can exist as therapeutically acceptable salts. The present invention includes compounds disclosed herein in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

[0226] The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are water or oil-soluble or dispersible and therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate,

propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds disclosed herein can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

[0227] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0228] Also provided herein are isotopically-substituted or -labeled compounds of Formula I or VI, wherein one or more atoms are replaced by one or more atoms having specific atomic mass or mass numbers. Examples of isotopes that can be incorporated into compounds disclosed herein include, but are not limited to, isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, sulfur, and chlorine (such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{18}F, ^{35}S and ^{36}Cl). Isotopically-labeled compounds of Formula I and prodrugs thereof, as well as isotopically-labeled, pharmaceutically acceptable salts of compounds of Formula I or VI and prodrugs thereof, are herein disclosed. Isotopically-labeled compounds are useful in assays of the tissue distribution of the compounds and their prodrugs and metabolites; preferred isotopes for such assays include ^{3}H and ^{14}C. In addition, in certain circumstances substitution with heavier isotopes, such as deuterium (^{2}H), can provide increased metabolic stability, which offers therapeutic advantages such as increased in vivo half-life or reduced dosage requirements. Isotopically-labeled compounds and prodrugs thereof can generally be prepared according to the methods described herein by substituting an isotopically-labeled reagent for a non-isotopically labeled reagent.

[0229] In other aspects, provided herein are intermediates and processes useful for preparing the intermediates below as well as the compounds of Formula I or VI, and pharmaceutically acceptable salts and prodrugs thereof.

[0230] In a similar manner, the present invention provides methods of preparing compounds of Formula I, that are based on the synthetic protocols outlined in Schemes 1 through 21 as well as methods well known by persons skilled in the art, and the more detailed particular examples presented below in the experimental section describing the examples. By following the general preparative methods discussed below, or employing variations or alternative methods, the compounds can be readily prepared by the use of chemical reactions and procedures known to those of skill in the art. Unless otherwise specified, the variables (*e.g.*, R groups) denoting groups in the general methods described below have the meanings as hereinbefore defined.

[0231] Those of skill in the art will recognize that compounds with each described functional group are generally prepared using slight variations of the below-listed general methods. Within the scope of each method, functional groups which are suitable to the reaction conditions are used. Functional groups which might interfere with certain reactions are presented in protected forms where necessary, and the removal of such protective groups is completed at appropriate stages by methods well known to those skilled in the art.

[0232] In certain cases compounds can be prepared from other compounds disclosed herein by elaboration, transformation, exchange and the like of the functional groups present. Such elaboration includes, but is not limited to, hydrolysis, reduction, oxidation, alkylation, acylation, esterification, amidation and dehydration. Such transformations can in some instances require the use of protecting groups by the methods disclosed in T. W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*; Wiley: New York, (1999), and incorporated herein by reference. Such methods would be initiated after synthesis of the desired compound or at another place in the synthetic route that would be readily apparent to one skilled in the art.

[0233] In another aspect, provided herein are synthetic intermediates useful for preparing the compounds of Formula I or VI, and pharmaceutically acceptable salts and prodrugs thereof, according

to the general preparative methods discussed below and other processes known to those of skill in the art.

[0234] When the following abbreviations and acronyms are used throughout the disclosure, they have the following meanings: $CDCl_3$, chloroform-*d*; CH_2Cl_2, methylene chloride; CH_3CN, acetonitrile; DIPEA, *N,N*-diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMF, *N,N*-dimethylformamide; DMSO, dimethylsulfoxide; Et, ethyl; Et_3N, triethylamine; EtOAc (or AcOEt), ethyl acetate; EtOH, ethanol; h, hour; HCl, hydrochloric acid; ^1H NMR, proton nuclear magnetic resonance; H_2SO_4, sulfuric acid; HPLC, high performance liquid chromatography; K_2CO_3, potassium carbonate; KOH, potassium hydroxide; LC-MS, liquid chromatography - mass spectroscopy; Me, methyl; MeOH, methanol; min, minute; MS ESI, mass spectroscopy with electrospray ionization; MsOH, methanesulfonic acid; NaH, sodium hydride; $NaHCO_3$, sodium bicarbonate; NaOH, sodium hydroxide; Na_2SO_4, sodium sulfate; NBS, N-bromosuccinimide; NCS, N-chlorosuccinimide; NH_3, ammonia; NIS, N-iodosuccinimide; Pd/C, palladium on carbon; $Pd(PPh_3)_4$, tetrakis(triphenylphosphine)palladium(0); R_f, retention factor; TBAF, tetrabutylammonium fluoride; TBAI, tetrabutylammonium iodide; TBDMS, *t*-butyldimethylsilyl; Tf_2O, trifluoromethanesulfonic anhydride; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLC, thin layer chromatography; TMS, trimethylsilyl; TMSCN, trimethylsilyl cyanide; TsOH, toluenesulfonic acid.

[0235] While it may be possible for compounds to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, provided herein are pharmaceutical formulations which comprise one or more of certain compounds disclosed herein, or one or more pharmaceutically acceptable salts, esters, prodrugs, amides, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in *Remington: The Science and Practice of Pharmacy*, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2003). The pharmaceutical compositions disclosed herein may be manufactured in any manner known in the art, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0236] A compound as provided herein can be incorporated into a variety of formulations for therapeutic administration, including solid, semi-solid, liquid or gaseous forms. The

formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Typically, these methods include the step of bringing into association a compound or a pharmaceutically acceptable salt, ester, amide, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0237] Formulations of the compounds disclosed herein suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0238] Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. 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. In addition, stabilizers may be added.

[0239] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses. Also provided are oral formulations in the form of powders and granules containing one or more compounds disclosed herein.

[0240] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0241] Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0242] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0243] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[0244] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

[0245] Certain compounds disclosed herein may be administered topically, that is by non-systemic administration. This includes the application of a compound disclosed herein externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[0246] Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 1% w/w of the formulation.

[0247] For administration by inhalation, compounds may be conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[0248] In one embodiment, a compound is prepared for delivery in a sustained-release, controlled release, extended-release, timed-release or delayed-release formulation, for example, in semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Current extended-release formulations include film-coated tablets,

multiparticulate or pellet systems, matrix technologies using hydrophilic or lipophilic materials and wax-based tablets with pore-forming excipients *(see*, for example, Huang, *et al. Drug Dev. Ind. Pharm*. 29:79 (2003); Pearnchob, *et al. Drug Dev. Ind. Pharm.* 29:925 (2003); Maggi, *et al. Eur. J. Pharm. Biopharm*. 55:99 (2003); Khanvilkar, *et al.*, *Drug Dev. Ind. Pharm.* 228:601 (2002); and Schmidt, *et al.*, *Int. J. Pharm.* 216:9 (2001)). Sustained-release delivery systems can, depending on their design, release the compounds over the course of hours or days, for instance, over 4, 6, 8, 10, 12, 16, 20, 24 hours or more. Usually, sustained release formulations can be prepared using naturally-occurring or synthetic polymers, for instance, polymeric vinyl pyrrolidones, such as polyvinyl pyrrolidone (PVP); carboxyvinyl hydrophilic polymers; hydrophobic and/or hydrophilic hydrocolloids, such as methylcellulose, ethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose; and carboxypolymethylene.

[0249] The sustained or extended-release formulations can also be prepared using natural ingredients, such as minerals, including titanium dioxide, silicon dioxide, zinc oxide, and clay (*see*, U.S. Patent 6,638,521, herein incorporated by reference). Exemplified extended release formulations that can be used in delivering a compound include those described in U.S. Patent Nos. 6,635,680; 6,624,200; 6,613,361; 6,613,358, 6,596,308; 6,589,563; 6,562,375; 6,548,084; 6,541,020; 6,537,579; 6,528,080 and 6,524,621, each of which is hereby incorporated herein by reference. Controlled release formulations of particular interest include those described in U.S. Patent Nos. 6,607,751; 6,599,529; 6,569,463; 6,565,883; 6,482,440; 6,403,597; 6,319,919; 6,150,354; 6,080,736; 5,672,356; 5,472,704; 5,445,829; 5,312,817 and 5,296,483, each of which is hereby incorporated herein by reference. Those skilled in the art will readily recognize other applicable sustained release formulations.

[0250] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. For topical administration, the agents can be formulated into ointments, creams, salves, powders or gels. In one embodiment, the transdermal delivery agent can be DMSO. Transdermal delivery systems can include, *e.g.*, patches. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. Exemplified transdermal delivery formulations that can find use with the compounds disclosed herein include those described in U.S. Patent Nos. 6,589,549; 6,544,548; 6,517,864; 6,512,010; 6,465,006; 6,379,696; 6,312,717 and 6,310,177, each of which are hereby incorporated herein by reference.

[0251] The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a

variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity. The dosage can be increased or decreased over time, as required by an individual patient. A patient initially may be given a low dose, which is then increased to an efficacious dosage tolerable to the patient. Typically, a useful dosage for adults may be from 5 to 2000 mg, but have been known to range from 0.1 to 500 mg/kg per day. By way of example, a dose may range from 1 to 200 mg, when administered by oral route; or from 0.1 to 100 mg or, in certain embodiments, 1 to 30 mg, when administered by intravenous route; in each case administered, for example, from 1 to 4 times per day. When a compound is administered in combination with another therapeutic agent, a useful dosage of the combination partner may be from 20% to 100% of the normally recommended dose, since, as discussed below, even doses of a given drug which would be subtherapeutic if administered on its own may be therapeutic when used in combination with another agent.

[0252] Dosage amount and interval can be adjusted individually to provide plasma levels of the active compounds that are sufficient to maintain therapeutic effect. In certain embodiments, therapeutically effective serum levels will be achieved by administering single daily doses, but efficacious multiple daily dose schedules may be used as well. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration. One having skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation. Additionally, applicable methods for determining an appropriate dose and dosing schedule for administration of compounds such as those disclosed herein are described, for example, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 11th Ed., Brunton, Lazo and Parker, Eds., McGraw-Hill (2006), and in *Remington: The Science and Practice of Pharmacy*, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2003), both of which are hereby incorporated herein by reference.

[0253] In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant

may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for HIV associated neurocognitive disease or dementia involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for neurocognitive disease or dementia or inflammation. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[0254] Specific, non-limiting examples of possible combination therapies include use of certain compounds disclosed herein with compounds used for treating diseases and conditions which can be affected by SGLT inhibition, such as antidiabetic agents, lipid-lowering/lipid-modulating agents, agents for treating diabetic complications, anti-obesity agents, antihypertensive agents, antihyperuricemic agents, and agents for treating chronic heart failure, atherosclerosis or related disorders.

[0255] In any case, the multiple therapeutic agents (at least one of which is a compound disclosed herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

[0256] Examples of agents to be used in combination with compounds disclosed herein include lithium, valproate and other agents used in neuroprotection, PAF receptor antagonists, antioxidants including mitochondrially-targeted antioxidants, activators of SIRT1 and other sirtuins, inhibitors of indoleamine 2,3 dehydrogenase (IDO), agents which enhance trans- blood brain barrier (BBB) uptake of drugs, including compounds that inhibit drug pumps at the BBB such as, for example, ritonavir; HAART drugs and other agents for use in HIV treatment; agents for the treatment of cardiovascular, heart, and metabolic disorders, such as HMG-CoA reductase inhibitors including statins, insulin and insulin mimetics, and glycogen synthase kinase-3 beta (GSK3β) inhibitors; agents which "normalize" mitochondrial function; antiinflammatory agents including PAF receptor antagonists or PAF acetylhydrolase, cyclooxygenase inhibitors

(including COX-2 selective and nonselective) such as aspirin, ibuprofen, naproxen, and celecoxib; and agents for blocking liver cell proliferation, such as JNK inhibitors.

[0257] Also provided are combinations of multiple agents, such as lithium plus a GSK3β blocker, to be used in combination with the compounds provided herein.

[0258] Additionally, agents for neuroprotection and/or neurogenesis include selective serotonin reuptake inhibitors SSRIs and small molecule agonists of neurotrophin receptors.

[0259] Any of the aforementioned agents may be combined with viral vectors that express genes intended to induce neural progenitor cells, as well.

[0260] Treatment with the compounds disclosed here in may also be effective when delivered along with deep-brain stimulation, such as in Parkinsonism and HIV-associated dementia/HIV-associated neurocognitive disorder.

[0261] Thus, in another aspect, certain embodiments provide methods for treating MLK3-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound disclosed herein effective to reduce or prevent said disorder in the subject, in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, certain embodiments provide therapeutic compositions comprising at least one compound disclosed herein in combination with one or more additional agents for the treatment of MLK3-mediated disorders.

[0262] Specific diseases to be treated by the compounds, compositions, and methods disclosed herein include: metabolic diseases such as type 1 and type 2 diabetes mellitus, hyperglycemia, diabetic complications (such as retinopathy, nephropathy, neuropathy, ulcers, micro- and macroangiopathies, gout and diabetic foot disease), insulin resistance, metabolic syndrome (Syndrome X), hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis (NASH), chronic heart failure, and atherosclerosis.

[0263] Compounds disclosed herein may also be useful for the treatment of inflammatory diseases such as bacterial sepsis, otitis media, endotoxemia, mucosal hyperplasia, inflammatory bowel disease, Crohn's disease, irritable bowel syndrome, and ulcerative colitis; and respiratory diseases and conditions such as asthma, chronic obstructive pulmonary disease (COPD), and acute inhalation-induced lung injury.

[0264] Compounds disclosed herein may also be useful for the treatment of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, lupus and Crohn's disease.

[0265] Compounds disclosed herein may also be useful for the treatment of proliferative disorders including cancers such as liver cancer. Furthermore, Compounds disclosed herein may

also be useful for the treatment of hepatitis, including viral hepatitis, and non-alcoholic steatohepatitis (NASH).

[0266] Compounds disclosed herein may also be useful for the treatment of ischemic injury, including stroke, cerebral ischemia/reperfusion, myocardial infarction, and ischemic heart disease.

[0267] Compounds disclosed herein may also be useful for the treatment of diseases and disorders of the nervous system such as Alzheimer's Disease (AD), Parkinson's Disease, HIV dementia, HIV associated neurocognitive disorder (HAND), neuroinflammatory diseases, and neuropathies including drug-induced peripheral neuropathy, and diabetic neuropathy, and HIV-associated neuropathy, ototoxicity and hearing loss, acute insults to the inner ear, including acoustic trauma, blast noise (for example, as experienced by military personnel), exposure to ototoxic chemotherapeutic agents for cancer therapy (such as cisplatin) and treatment with aminoglycoside antibiotics. Compounds disclosed herein may also be useful for the treatment of traumatic brain injury including stroke.

[0268] Compounds disclosed herein may also be useful for the treatment of pain including inflammatory pain, neuropathic pain, back pain including discogenic pain, the pain of arthritis and autoimmune disorders such as rheumatoid arthritis, and cancer pain including pain due to bone metastasis.

[0269] Compounds disclosed herein may also be useful for the treatment of psychological disorders including depression or major depressive disorder (MDD), bipolar disorder, and post-traumatic stress disorder.

[0270] Compounds disclosed herein may also be useful for enhancement of stem cell based therapies in the central nervous system (CNS).

EXAMPLES

[0271] The following examples are set forth below to illustrate the methods and results according to the disclosed subject matter. These examples are not intended to be inclusive of all aspects of the subject matter disclosed herein, but rather to illustrate representative methods and results. These examples are not intended to exclude equivalents and variations of the present invention which are apparent to one skilled in the art.

[0272] Efforts have been made to ensure accuracy with respect to numbers (*e.g.*, amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric. There are numerous variations and combinations of reaction

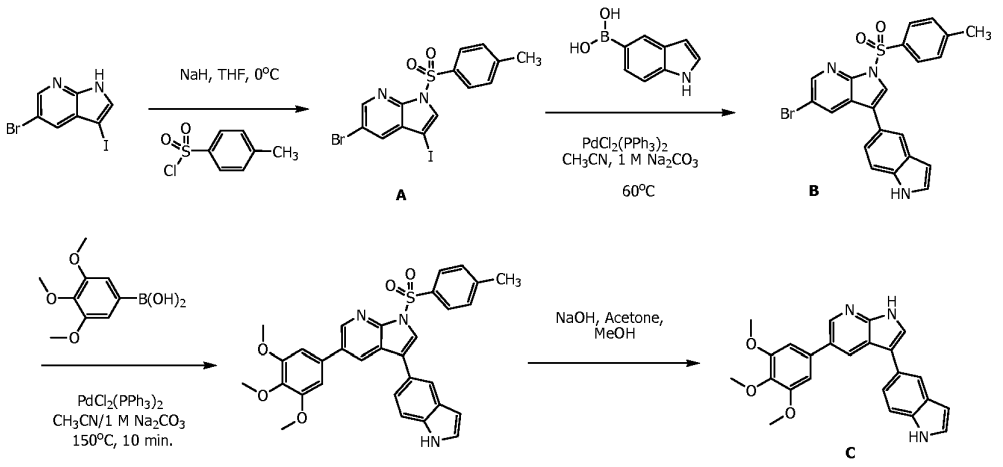
conditions, *e.g.*, component concentrations, temperatures, pressures, and other reaction ranges and conditions that can be used to optimize the product purity and yield obtained from the described process.

[0273] The structures of compounds synthesized in the examples below were confirmed using the following procedures. LC-MS/UV/ELS analysis was performed on instrumentation consisting of Shimadzu LC-10AD vp series HPLC pumps and dual wavelength UV detector, a Gilson 215 autosampler, a Sedex 75c evaporative light scattering (ELS) detector, and a PE/Sciex API 150EX mass spectrometer. The ELS detector was set to a temperature of 40°C, a gain setting of 7, and a N_2 pressure of 3.3 atm. The Turbo IonSpray source was employed on the API 150 with an ion spray voltage of 5 kV, a temperature of 300 °C, and orifice and ring voltages of 5 V and 175 V respectively. Positive ions were scanned in Q1 from 160 to 650 m/z. 5.0 μL injections were performed for each sample, on a Phenomenex Gemini 5μm C18 column. Mobile phases consisted of 0.05% formic acid in both HPLC grade water (A) and HPLC grade acetonitrile (B). 5.0 μL injections were performed for each sample, using gradient elution from 5% B to 100% B in 4 min at a flow rate of 2.0 mL/min with a final hold at 100% B of 1.8 min. UV and ELS data is collected for 4.5 min. Routine one-dimensional NMR spectroscopy was performed on a 300 MHz Varian Mercury-Plus spectrometer. The samples were dissolved in deuterated solvents obtained from Cambridge Isotope Laboratories, Inc., and transferred to 5 mm ID NMR tubes. The spectra were acquired at 293 K. The chemical shifts were recorded on the ppm scale and were referenced to the appropriate solvent signals, such as 2.49 ppm for DMSO-*d6*, 1.93 ppm for CD_3CN, 3.30 ppm for CD_3OD, 5.32 ppm for CD_2Cl_2 and 7.26 ppm for $CDCl_3$ for ^1H spectra.

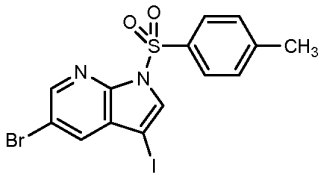
[0274] Other equipment and techniques standard in the art of chemical analysis and characterization may be used.

Example 1

Scheme 1

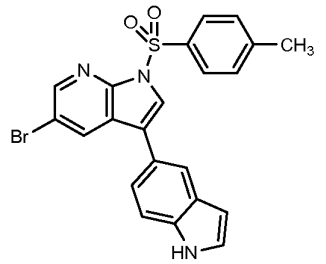


Preparation of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate A)



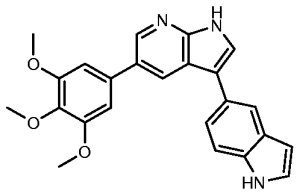
[0275] To a stirred solution of 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (0.70 g, 2.2 mmol) in 15 mL of anhydrous THF cooled to 0°C with an ice bath was added NaH [60% dispersion in mineral oil] (0.13 g, 3.3 mmol). The reaction mixture was stirred for 20 min at 0°C, after which *p*-toluenesulfonyl chloride (0.47 g, 2.4 mmol) was added. The resulting mixture was stirred at 0°C for 1.5 hr, after which cold 0.5 M HCl (20 mL) was added. The mixture was partitioned between EtOAc and 0.5 M HCl, after which the organic layer was separated, dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield a residue that was triturated with 20% CH_2Cl_2 in hexanes to yield the title compound (0.84 g, 81%) as a light yellow powder. ^{1}H NMR (DMSO-*d6*, 300MHz) δ 8.51 (d, *J* = 2.1 Hz, 1H), 8.22 (s, 1H), 8.02 (d, *J* = 1.2 Hz, 1 H), 8.00 (d, *J* = 5.1 Hz, 2H), 7.44 (dd, *J* = 8.7 Hz, 0.6 Hz, 2H), 2.35 (s, 3H); MS ESI (m/z): 477.0/479.0 $(M+1)^+$, calc. 476.

Preparation of 5-bromo-3-(1H-indol-5-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (Intermediate B)



[0276] To a stirred suspension of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.35 g, 0.73 mmol) and 1*H*-indol-5-ylboronic acid (0.14 mg, 0.88 mmol) in CH_3CN (10 mL) was added 1 M Na_2CO_3 (10 mL) followed by bis(triphenylphosphine)palladium(II) dichloride (0.050 g, 0.071 mmol). The resulting mixture was stirred overnight at 60°C. After the mixture was evaporated to dryness *in vacuo*, it was dissolved in DMF (3 mL), absorbed onto Celite, and dried. The residue was purified via silica gel chromatography using CH_2Cl_2 as the eluent to obtain the title compound (0.26 g, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.48 (d, *J* = 2.1 Hz, 1H), 8.27 (bs, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 8.08 (d, *J* = 8.1 Hz), 7.85 (s, 1H), 7.81 (m, 1H), 7.50 (d, *J* = 8.7 Hz, 1 H), 7.37 (dd, *J* = 1.8, 8.4 Hz), 7.30 (m, 3H), 6.63 (m, 1 H), 2.39 (s, 3H); MS ESI (m/z): 466.2/468.2 $(M+1)^+$, calc. 465.

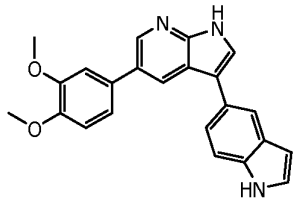
Preparation of 3-(1*H*-indol-5-yl)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (Compound C)



[0277] To a solution of 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (65 mg, 0.14 mmol) in CH_3CN (1 mL) in a Personal Chemistry microwave reaction vial was added 3,4,5-trimethoxyphenylboronic acid (30 mg, 0.14 mmol), bis(triphenylphosphine)-palladium(II) dichloride (7.0 mg, 0.010 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 10 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL) and acetone (2 mL), and 2 M NaOH (1.5 mL) was added. The resulting mixture was stirred at 65°C for 30 min, after which it was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to give a residue purified via preparatory HPLC to give the title compound as a white solid. ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.78 (s, 1H), 11.03 (s, 1 H), 8.51 (d, *J* = 2.1 Hz, 1H), 8.36 (d, *J* = 1.8 Hz, 1H), 7.86 (s, 1H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.45 (s, 2H), 7.32 (m, 1H), 6.92 (s, 2H), 6.45 (m, 1 H), 3.85 (s, 6H), 3.70 (s, 3H); HPLC retention time: 2.04 minutes; MS ESI (m/z): 400.4 $(M+1)^+$, calc. 399.

Example 2

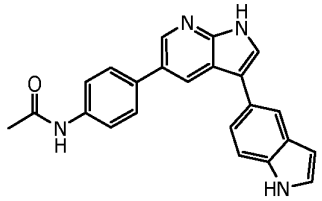
Preparation of 5-(3,4-dimethoxyphenyl)-3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (Compound D)



[0278] Compound D was prepared by a method analogous to that described in *Example 1* by substituting 3,4-dimethoxyphenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 2.33 minutes. MS ESI (m/z): 370.2 $(M+H)^+$, calc. 369.

Example 3

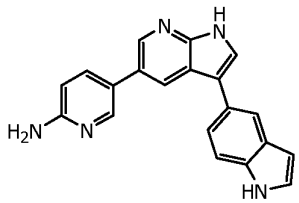
Preparation of *N*-(4-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)acetamide (Compound E)



[0279] Compound E was prepared by a method analogous to that described in *Example 1* by substituting 4-acetamidophenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 1.86 minutes. MS ESI (m/z): 367.4 $(M+H)^+$, calc.366.

Example 4

Preparation of 5-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridin-2-amine (Compound F)

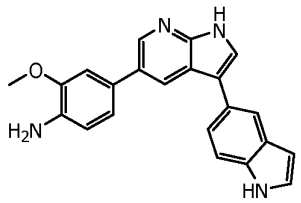


[0280] Compound F was prepared by a method analogous to that described in *Example 1* by substituting 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine for 3,4,5-

trimethoxyphenylboronic acid in the reaction with intermediate B. ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.73 (d, *J* = 1.8 Hz, 1H), 11.05 (s, 1 H), 8.43 (d, *J* = 2.4 Hz, 1H), 8.29 (d, *J* = 1.8 Hz, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 7.88 (s, 1H), 7.76 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.46 (s, 2H), 7.33 (m, 1H), 6.55 (dd, *J* = 0.6, 8.7 Hz, 1H), 6.46 (m, 1 H), 5.99 (s, 2 H). HPLC retention time: 1.10 minutes. MS ESI (m/z): 326.2 $(M+H)^+$, calc. 325.

Example 5

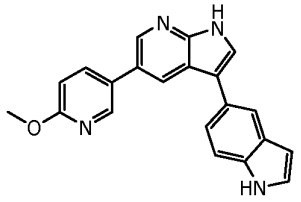
Preparation of 4-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-methoxyaniline (Compound G)



[0281] Compound G was prepared by a method analogous to that described in *Example 1* by substituting 4-amino-3-methoxyphenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 1.54 minutes. MS ESI (m/z): 355.4 $(M+H)^+$, calc. 354.

Example 6

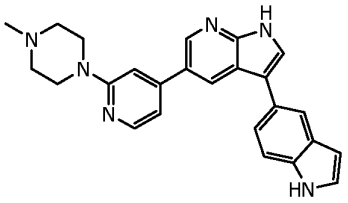
Preparation of 3-(1*H*-indol-5-yl)-5-(6-methoxypyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (Compound H)



[0282] Compound H was prepared by a method analogous to that described in *Example 1* by substituting 6-methoxypyridin-3-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 2.16 minutes. MS ESI (m/z): 341.4 $(M+H)^+$, calc. 340.

Example 7

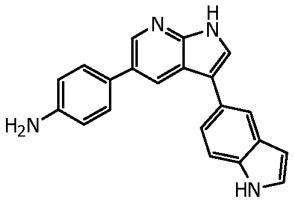
Preparation of 3-(1*H*-indol-5-yl)-5-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (Compound I)



[0283] Compound I was prepared by a method analogous to that described in *Example 1* by substituting 2-(4-methylpiperazin-1-yl)pyridin-4-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 1.37 minutes. MS ESI (m/z): 409.4 $(M+H)^+$, calc. 408.

Example 8

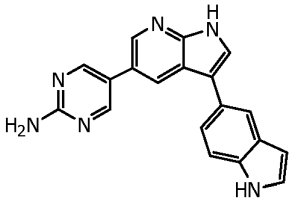
Preparation of 4-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)aniline (Compound J)



[0284] Compound J was prepared by a method analogous to that described in *Example 1* by substituting 4-aminophenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 1.47 minutes. MS ESI (m/z): 325.4 $(M+H)^+$, calc. 324.

Example 9

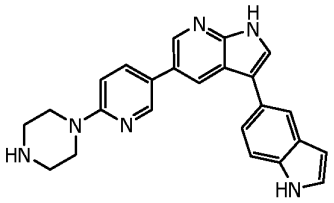
Preparation of 5-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyrimidin-2-amine (Compound K)



[0285] Compound K was prepared by a method analogous to that described in *Example 1* by substituting 2-aminopyrimidin-5-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 1.81 minutes. MS ESI (m/z): 327.2 $(M+H)^+$, calc. 326.

Example 10

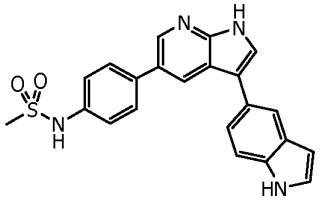
Preparation of 3-(1*H*-indol-5-yl)-5-(6-(piperazin-1-yl)pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (Compound L)



[0286] Compound L was prepared by a method analogous to that described in *Example 1* by substituting 6-(piperazin-1-yl)pyridin-3-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 1.15 minutes. MS ESI (m/z) 395.4 $(M+H)^+$, calc. 394.

Example 11

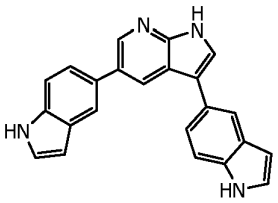
Preparation of *N*-(4-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)methanesulfonamide (Compound M)



[0287] Compound M was prepared by a method analogous to that described in *Example 1* by substituting 4-(methylsulfonamido)phenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 1.99 minutes. MS ESI (m/z): 403.4 $(M+H)^+$, calc. 402.

Example 12

Preparation of 3,5-di(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (Compound N)

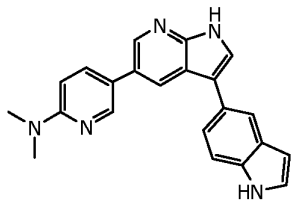


[0288] Compound N was prepared by a method analogous to that described in *Example 1* by substituting 1*H*-indol-5-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction

with intermediate B. HPLC retention time: 2.01 minutes. MS ESI (m/z): 349.2 $(M+H)^+$, calc. 348.

Example 13

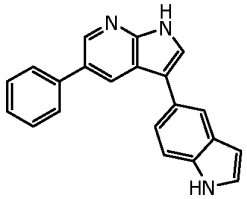
Preparation of 5-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-N,N-dimethylpyridin-2-amine (Compound O)



[0289] Compound O was prepared by a method analogous to that described in *Example 1* by substituting 6-(dimethylamino)pyridin-3-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 1.58 minutes. MS ESI (m/z): 354.4 $(M+H)^+$, calc. 353.

Example 14

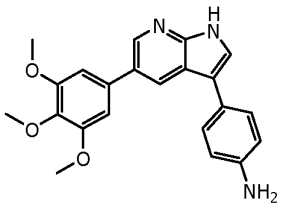
Preparation of 3-(1*H*-indol-5-yl)-5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (Compound P)



[0290] Compound P was prepared by a method analogous to that described in *Example 1* by substituting phenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate B. HPLC retention time: 2.49 minutes. MS ESI (m/z): 310.2 $(M+H)^+$, calc. 309.

Example 15

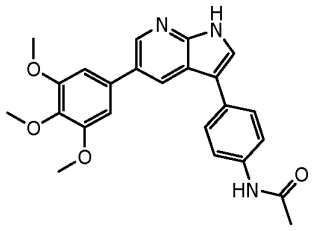
Preparation of 4-(5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)aniline (Compound Q)



[0291] Compound Q was prepared by a method analogous to that described in *Example 1* by substituting 4-aminophenylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A. HPLC retention time: 1.45 minutes. MS ESI (m/z): 376.4 $(M+H)^+$, calc. 375.

Example 16

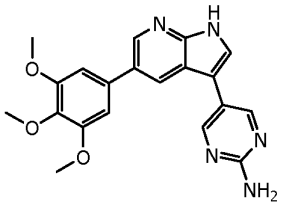
Preparation of *N*-(4-(5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenyl)acetamide (Compound R)



[0292] Compound R was prepared by a method analogous to that described in *Example 1* by substituting 4-acetamidophenylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A. HPLC retention time: 1.98 minutes. MS ESI (m/z): 418.6 $(M+H)^+$, calc. 417.

Example 17

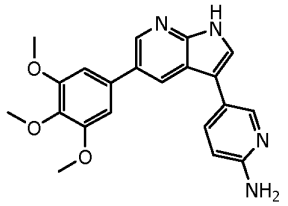
Preparation of 5-(5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyrimidin-2-amine (Compound S)



[0293] Compound S was prepared by a method analogous to that described in *Example 1* by substituting 2-aminopyrimidin-5-ylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A. HPLC retention time: 1.98 minutes. MS ESI (m/z): 378.4 $(M+H)^+$, calc. 377.

Example 18

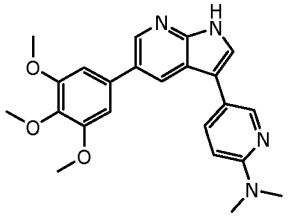
Preparation of 5-(5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyridin-2-amine (Compound T)



[0294] Compound T was prepared by a method analogous to that described in *Example 1* by substituting 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A. ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.82 (s, 1H), 8.53 (d, *J* = 1.8 Hz, 1H), 8.31 (d, *J* = 1.8, 1 H), 8.28 (d, *J* = 1.5 Hz), 7.76 (dd, *J* = 2.1, 8.4 Hz, 1 H), 7.70 (d, *J* = 2.4 Hz, 1H), 6.95 (s, 2H), 6.54 (d, J = 8.4 Hz, 1 H), 5.87 (s, 2H), 3.86 (s, 6H), 3.68 (s, 3H); HPLC retention time: 1.10 minutes. MS ESI (m/z): 377.4 $(M+H)^+$, calc. 376.

Example 19

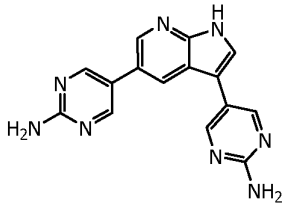
Preparation of *N*,*N*-dimethyl-5-(5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyridin-2-amine (Compound U)



[0295] Compound U was prepared by a method analogous to that described in *Example 1* by substituting 6-(dimethylamino)pyridin-3-ylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A. HPLC retention time: 1.43 minutes. MS ESI (m/z): 405.6 $(M+H)^+$, calc. 404.

Example 20

Preparation of 5,5'-(1*H*-pyrrolo[2,3-*b*]pyridine-3,5-diyl)dipyrimidin-2-amine (Compound W)

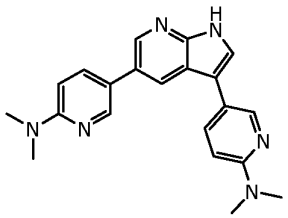


Compound W was prepared by a method analogous to that described in *Example 1* by substituting 2-aminopyrimidin-5-ylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction

with Intermediate A and 2-aminopyrimidin-5-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with Intermediate B. HPLC retention time: 1.17 minutes. MS ESI (m/z): 305.2 $(M+H)^+$, calc. 304.

Example 21

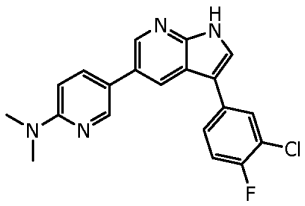
Preparation of 5,5'-(1*H*-pyrrolo[2,3-*b*]pyridine-3,5-diyl)bis(*N*,*N*-dimethylpyridin-2-amine) (Compound X)



[0296] Compound X was prepared by a method analogous to that described in *Example 1* by substituting 6-(dimethylamino)pyridin-3-ylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A and 6-(dimethylamino)pyridin-3-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with Intermediate B. HPLC retention time: 1.17 minutes. MS ESI (m/z): 359.4 $(M+H)^+$, calc. 358.

Example 22

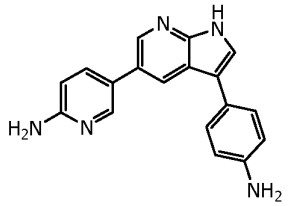
Preparation of 5-(3-(3-chloro-4-fluorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*,*N*-dimethylpyridin-2-amine (Compound Y)



[0297] Compound Y was prepared by a method analogous to that described in *Example 1* by substituting 3-chloro-4-fluorophenylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A and 6-(dimethylamino)pyridin-3-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with Intermediate B. HPLC retention time: 1.73 minutes. MS ESI (m/z): 367.2 $(M+H)^+$, calc. 366.

Example 23

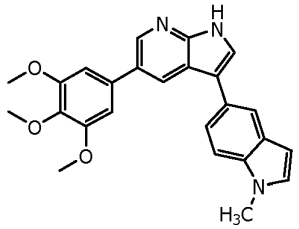
Preparation of 5-(3-(4-aminophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridin-2-amine (Compound Z)



[0298] Compound Z was prepared by a method analogous to that described in *Example 1* by substituting 4-aminophenylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A and 6-aminopyridin-3-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with Intermediate B. HPLC retention time: 0.68 minutes. MS ESI (m/z): 302.4 $(M+H)^+$, calc. 301.

Example 24

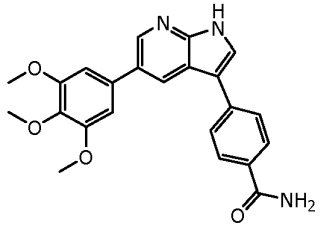
Preparation of 3-(1-methyl-1*H*-indol-5-yl)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (Compound AA)



[0299] Compound AA was prepared by a method analogous to that described in *Example 1* by substituting 1-methyl-1*H*-indol-5-ylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A. HPLC retention time: 2.29 minutes. MS ESI (m/z): 414.4 $(M+H)^+$, calc. 413.

Example 25

Preparation of 4-(5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzamide (Compound AB)

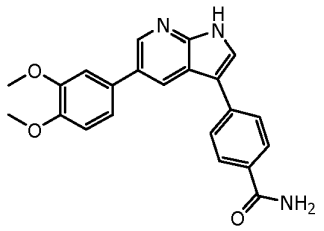


[0300] Compound AB was prepared by a method analogous to that described in *Example 1* by substituting 4-carbamoylphenylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction

with Intermediate A. HPLC retention time: 1.64 minutes. MS ESI (m/z): 404.6 $(M+H)^+$, calc. 403.

Example 26

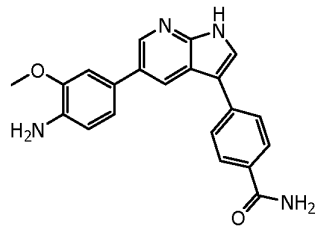
Preparation of 4-(5-(3,4-dimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzamide (Compound AC)



[0301] Compound AC was prepared by a method analogous to that described in *Example 1* by substituting 4-carbamoylphenylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A and 3,4-dimethoxyphenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with Intermediate B. HPLC retention time: 1.60 minutes. MS ESI (m/z): 374.2 $(M+H)^+$, calc. 373.

Example 27

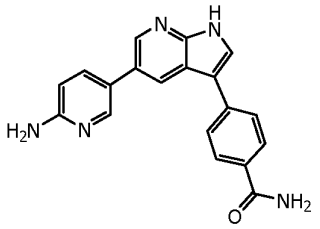
Preparation of 4-(5-(4-amino-3-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzamide (Compound AD)



[0302] Compound AD was prepared by a method analogous to that described in *Example 1* by substituting 4-carbamoylphenylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A and 4-amino-3-methoxyphenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with Intermediate B. HPLC retention time: 1.46 minutes. MS ESI (m/z): 359.2 $(M+H)^+$, calc. 358.

Example 28

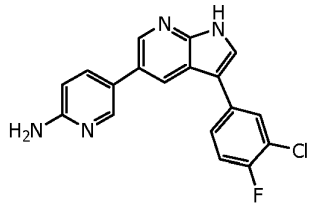
Preparation of 4-(5-(6-aminopyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzamide (Compound AE)



[0303] Compound AE was prepared by a method analogous to that described in *Example 1* by substituting 4-carbamoylphenylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine for 3,4,5-trimethoxyphenylboronic acid in the reaction with Intermediate B. HPLC retention time: 1.13 minutes. MS ESI (m/z): 330.4 $(M+H)^+$, calc. 329.

Example 29

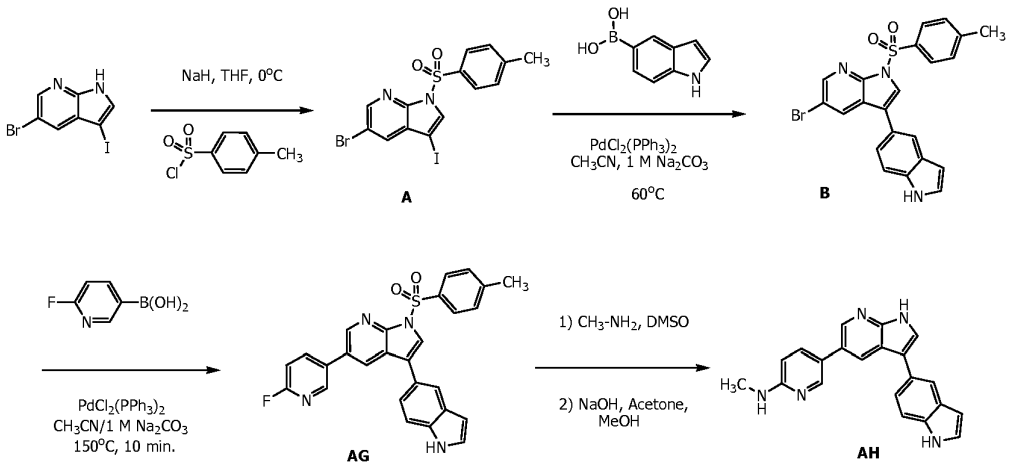
Preparation of 5-(3-(3-chloro-4-fluorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyridin-2-amine (Compound AF)



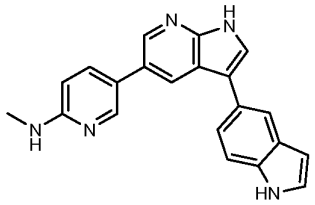
[0304] Compound AF was prepared by a method analogous to that described in *Example 1* by substituting 3-chloro-4-fluorophenylboronic acid for 1*H*-indol-5-ylboronic acid in the reaction with Intermediate A and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine for 3,4,5-trimethoxyphenylboronic acid in the reaction with Intermediate B. HPLC retention time: 1.47 minutes. MS ESI (m/z): 339.4 $(M+H)^+$, calc. 338.

Example 30

Scheme 2



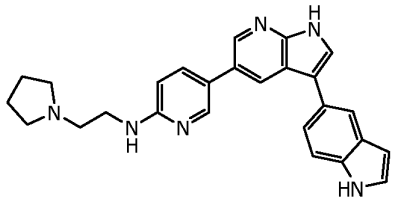
Preparation of 5-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-methylpyridin-2-amine (Compound AH)



[0305] To a solution of 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (40 mg, 0.09 mmol) in CH_3CN (1 mL) in a Personal Chemistry microwave reaction vial was added 6-fluoropyridin-3-ylboronic acid (12 mg, 0.09 mmol), bis(triphenylphosphine)-palladium(II) dichloride (5.0 mg, 0.007 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 10 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo* to give intermediate Q. The residue was dissolved in DMSO (0.5 mL) and methylamine hydrochloride salt (29 mg, 0.43 mmol), and K_2CO_3 (95 mg, 0.70 mmol) were added. The resulting mixture was stirred at 80°C for 48 hr, after which it was diluted with DMF (0.5 mL), filtered, and subjected to preparative HPLC to yield the title compound (6.0 mg, 21%). ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.77 (s, 1H), 11.07 (s, 1 H), 8.46 (d, *J* = 2.1 Hz, 1H), 8.34 (dd, *J* = 2.4, 9.3 Hz, 1H), 7.90 (s, 1H), 7.86 (m, 1H), 7.74 (d, *J* = 2.7 Hz, 1 H), 7.47 (s, 2 H), 7.35 (s, 1 H), 6.80 (s, 1 H), 6.63 (d, J = 8.4 Hz, 1 H), 6.48 (m , 1H), 2.84 (d, J = 4.5 Hz, 1 H). HPLC retention time: 1.10 minutes; HPLC retention time: 1.56 minutes; MS ESI (m/z): 340.2 $(M+1)^+$, calc. 339.

Example 31

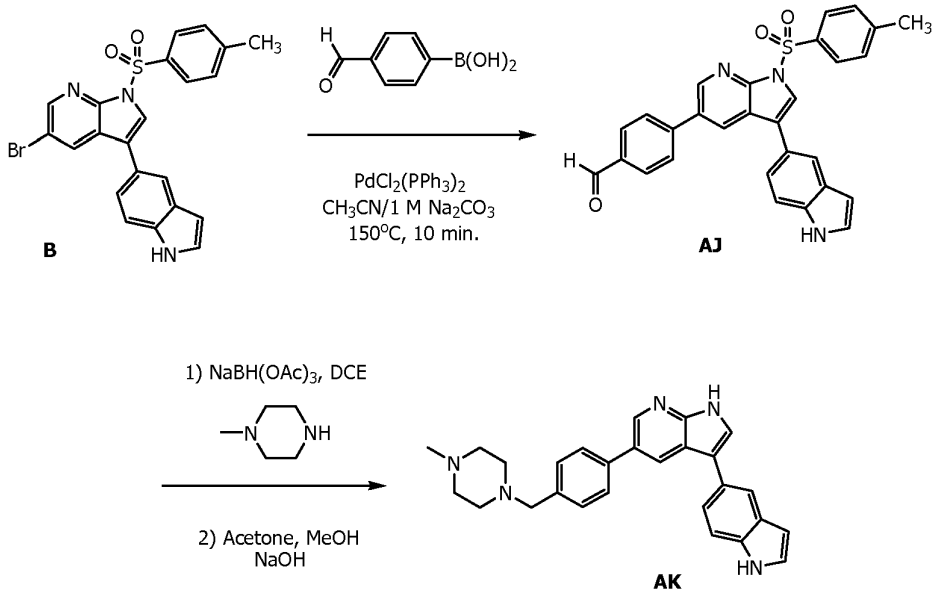
Preparation of 5-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-(2-(pyrrolidin-1-yl)ethyl)pyridin-2-amine (Compound AI)



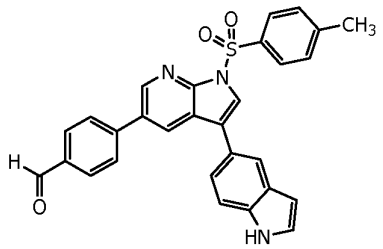
[0306] Compound AI was prepared by a method analogous to that described in *Example 15* by substituting 2-(pyrrolidin-1-yl)ethanamine for methylamine hydrochloride salt in the reaction with intermediate Q. HPLC retention time: 1.58 minutes. MS ESI (m/z): 354.4 $(M+H)^+$, calc. 353.

Example 32

Scheme 3

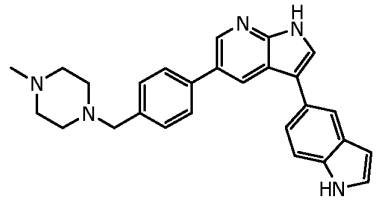


Preparation of 4-(3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzaldehyde (Intermediate AJ)



[0307] To a solution of 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine [Intermediate **B**] (0.20 g, 0.43 mmole) in CH_3CN (4 mL) in a Personal Chemistry microwave reaction vial was added 4-formylphenylboronic acid (64 mg, 0.43 mmol), bis(triphenylphosphine)-palladium(II) dichloride (40 mg, 0.057 mmol), and 1 M Na_2CO_3 (2 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 10 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and partitioned between EtOAc and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give Intermediate **AJ**. HPLC retention time: 3.01 minutes. MS ESI (m/z): 492.4 $(M+H)^+$, calc. 491.

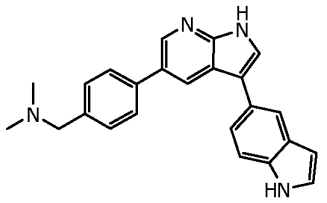
Preparation of 3-(1*H*-indol-5-yl)-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (Compound AK)



[0308] To a solution of 4-(3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzaldehyde [Intermediate **AJ**] (0.11 g, 0.214 mmol) in CH_2Cl_2 (3 mL) was added 1-methylpiperazine (40 μL, 0.40 mmol) and sodium triacetoxyborohydride (68 mg, 0.32 mmol). The reaction mixture was stirred for 1 hr at room temperature, after which it was partitioned between CH_2Cl_2 and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in 3:2 MeOH:acetone (5 mL), and 2 M NaOH (1.5 mL) was added. The resulting mixture was stirred at 65°C for 30 min, after which it was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to provide a residue that was subjected to preparatory HPLC to yield the title compound. HPLC retention time: 1.63 minutes; MS ESI (m/z) 422.4 $(M+1)^+$, calc. 421.

Example 33

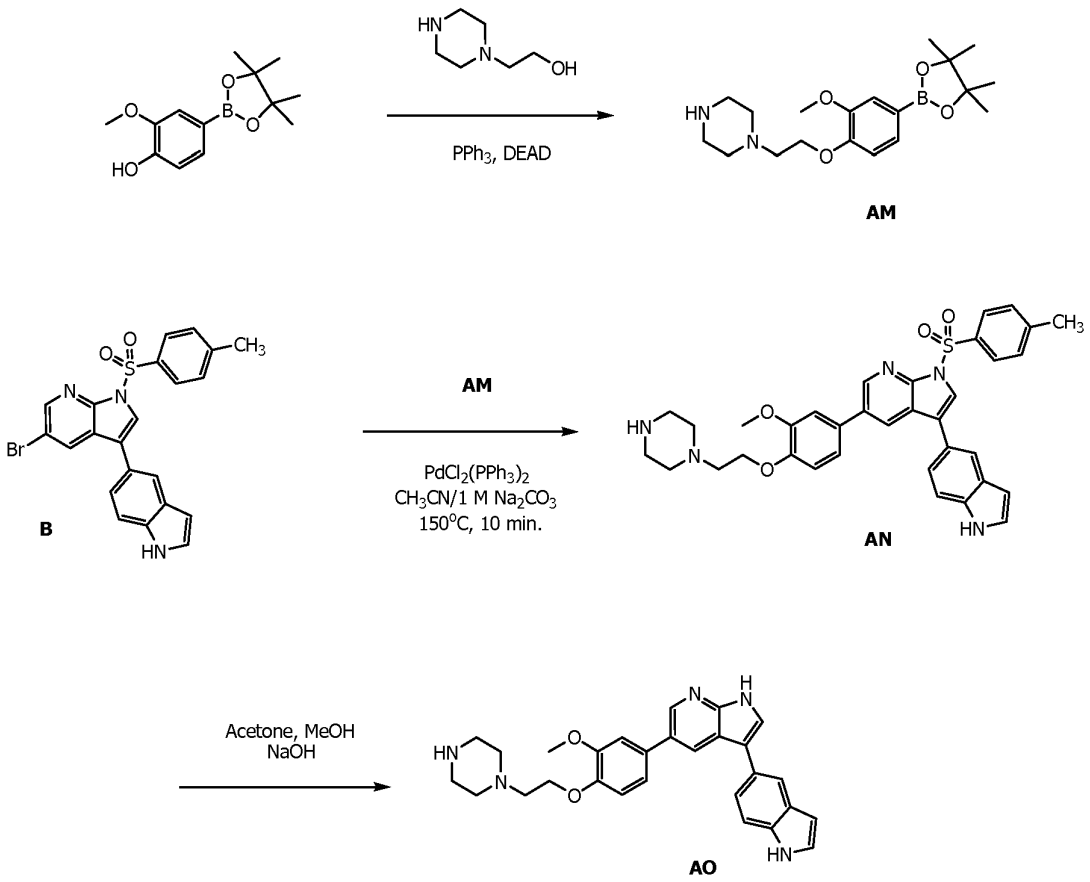
Preparation of 1-(4-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)-*N*,*N*-dimethylmethanamine (Compound AL)



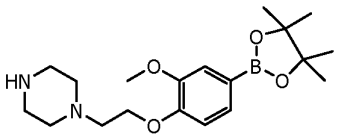
[0309] Compound **AL** was prepared by a method analogous to that described in *Example 33* by substituting dimethylamine (2 M solution in THF) for 1-methylpiperazine in the reaction with intermediate T. HPLC retention time: 1.66 minutes. MS ESI (m/z): 367.4 $(M+H)^+$, calc. 366.

Example 34

Scheme 4

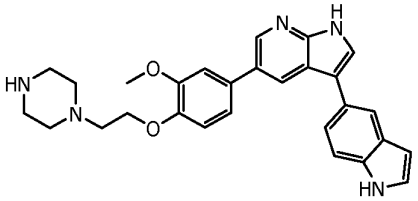


Preparation of 1-(2-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)piperazine (Intermediate AM)



[0310] To a solution of 2-(piperazin-1-yl)ethanol (0.78 mL, 6.0 mmol) and triphenylphosphine (1.6 g, 6.0 mmol) in anhydrous THF (20 mL) at 0°C was added diethyl azodicarboxylate (0.95 mL, 6.0 mmol), followed by 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.0 g, 4.0 mmol). After stirring for 4 h at rt, additional triphenylphosphine (1.6 g, 6.0 mmol) and diethyl azodicarboxylate (0.95 mL, 6.0 mmol) were added. After stirring for an additional 2 h, the resulting mixture was evaporated to dryness *in vacuo* and the residue was purified via silica gel chromatography eluting with 15% MeOH in CH_2Cl_2 to yield a yellow oil (1.89 g) which contained approximately 60% of the title compound by HPLC analysis. HPLC retention time: 1.01 minutes. MS ESI (m/z): 363.6 $(M+H)^+$, calc. 362.

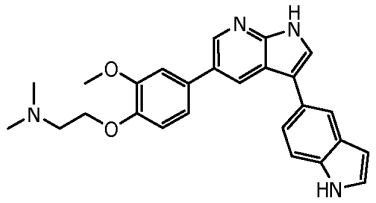
Preparation of 3-(1*H*-indol-5-yl)-5-(3-methoxy-4-(2-(piperazin-1-yl)ethoxy)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (Compound AO)



[0311] To a solution of 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate B) (92 mg, 0.20 mmol) in CH_3CN (2 mL) in a Personal Chemistry microwave reaction vial was added 1-(2-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)piperazine (Intermediate AM) (72 mg, 0.20 mmol), bis(triphenylphosphine)-palladium(II) dichloride (20 mg, 0.028 mmol), and 1 M Na_2CO_3 (2 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 25 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo* to give Intermediate **AN**. The residue was dissolved in MeOH (3 mL) and acetone (2 mL), and 2 M NaOH (1.5 mL) was added. The resulting mixture was stirred at 50°C for 2 h, after which it was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to give a residue that was subjected to preparatory HPLC to yield the title compound. HPLC retention time: 1.29 minutes; MS ESI (m/z) 468.6 $(M+1)^+$, calc. 467.

Example 35

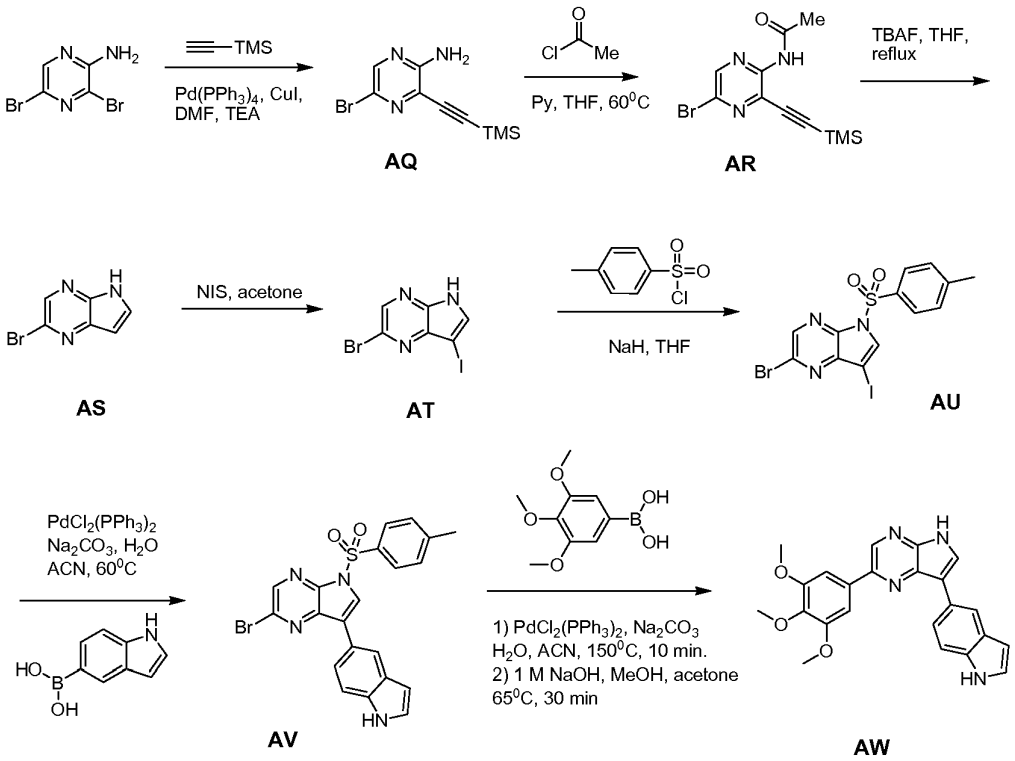
Preparation of 2-(4-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-methoxyphenoxy)-*N*,*N*-dimethylethanamine (Compound AP)



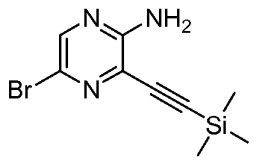
[0312] Compound AP was prepared by a method analogous to that described in *Example 36* by substituting 2-(dimethylamino)ethanol for 2-(piperazin-1-yl)ethanol in the reaction with 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol. HPLC retention time: 1.20 minutes. MS ESI (m/z): 427.2 $(M+H)^+$, calc. 426.

Example 36

Scheme 5

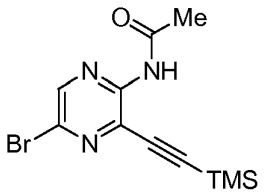


Preparation of 5-bromo-3-((trimethylsilyl)ethynyl)pyrazin-2-amine (Intermediate AQ)



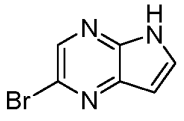
[0313] To a solution of 3,5-dibromopyrazin-2-amine (10 g, 40 mmol), copper(I) iodide (0.91 g, 4.7 mmol), diisopropylethylamine (53 mL, 0.55 mol), and tetrakis(triphenylphosphine)-palladium(0) (2.3 g, 1.9 mmol) in DMF (120 mL) that was de-gassed with Ar was added trimethylsilylacetylene (6.7 mL, 48 mmol). The resulting mixture was stirred under an Ar atmosphere for 1 h at 120°C, after which it was evaporated to dryness *in vacuo*. The residue was subjected to silica gel chromatography eluting with 35% EtOAc in hexanes to give a brown oil that was triturated with hexanes to give the title compound (5.0 g, 47%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (s, 1H), 5.10 (s, 2 H), 0.28 (s, 9H). HPLC retention time: 2.75 minutes. MS ESI (m/z): 270.0, 272.0 $(M+H)^+$, calc. 269.

Preparation of *N*-(5-bromo-3-((trimethylsilyl)ethynyl)pyrazin-2-yl)acetamide (Intermediate AR)



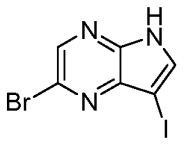
[0314] To a solution of 5-bromo-3-((trimethylsilyl)ethynyl)pyrazin-2-amine (5.0 g, 19 mmol) and pyridine (3.8 mL, 46 mmol) in anhydrous THF (75 mL) was added acetyl chloride (1.6 mL, 23 mmol) in a drop-wise manner. After stirring for 48 hr at rt, additional acetyl chloride (0.4 mL, 6 mmol) was added and the mixture was stirred for an additional 48 hr at rt. The solvent was removed *in vacuo*, and the residue was diluted with 30% EtOAc in hexanes. The mixture was filtered, and the filtrate was purified via silica gel chromatography eluting with 30% EtOAc in hexanes to give a yellow-brown solid (1.8 g, 31%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.34 (s, 1H), 8.08 (s, 1 H), 2.46 (s, 3 H), 0.32 (s, 9H). HPLC retention time: 2.29 minutes. MS ESI (m/z): 312.2, 314.2 $(M+H)^+$, calc. 311.

Preparation of 2-bromo-5*H*-pyrrolo[3,2-*b*]pyrazine (Intermediate AS)



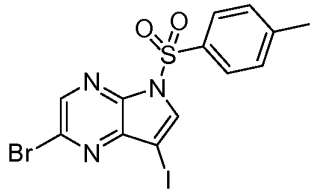
[0315] A solution of *N*-(5-bromo-3-((trimethylsilyl)ethynyl)pyrazin-2-yl)acetamide [Intermediate **AR**] (2.6 g, 8.4 mmol) and tetrabutylammonium fluoride [1 M in THF] (18 mL, 18 mmol) in anhydrous THF (26 mL) was heated at 75°C for 20 h, after which it was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to yield a residue that was purified via silica gel chromatography eluting with 30% EtOAc in hexanes to give the title compound as a tan solid (0.69 g, 42%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.88 (bs, 1H), 8.34 (s, 1 H), 7.62 (t, J = 3.3 Hz, 1 H), 6.71 (dd, J = 3.6 Hz, 3.9 Hz, 1 H). HPLC retention time: 1.73 minutes. MS ESI (m/z): 198.2, 200.2 $(M+H)^+$, calc. 197.

Preparation of 2-bromo-7-iodo-5*H*-pyrrolo[3,2-*b*]pyrazine (Intermediate AT)



[0316] To a solution of 2-bromo-5*H*-pyrrolo[3,2-*b*]pyrazine [Intermediate **AS**] (0.68 g, 3.4 mmol) in acetone (17 mL) was added *N*-iodosuccinimide (0.82 g, 3.6 mmol) and the resulting mixture was stirred for 4 h at rt. The mixture was evaporated *in vacuo* to yield a residue that was purified via silica gel chromatography eluting with 40% THF in hexanes to give the title compound as a yellow solid (0.99 g, 89%). ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 12.82 (s, 1H), 8.42 (s, 1 H), 8.20 (s, 1 H). HPLC retention time: 2.23 minutes. MS ESI (m/z): 324.0, 326.0 $(M+H)^+$, calc. 323.

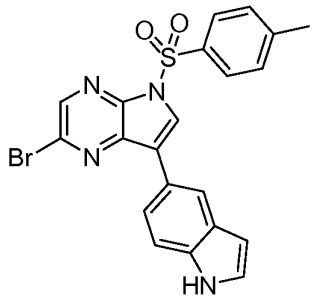
Preparation of 2-bromo-7-iodo-5-tosyl-5*H*-pyrrolo[3,2-*b*]pyrazine (Intermediate AU)



[0317] To a stirred solution of 2-bromo-7-iodo-5*H*-pyrrolo[3,2-*b*]pyrazine [Intermediate **AT**] (1.1 g, 3.5 mmol) in anhydrous THF (20 mL) cooled to 0°C was added NaH [60% dispersion in mineral oil] (0.17 g, 4.3 mmol). The reaction mixture was stirred for 20 min at 0°C, after which *p*-toluenesulfonyl chloride (0.73 g, 3.8 mmol) in THF (8 mL) was added. The resulting mixture was stirred at rt for 3 hr, after which it was diluted with EtOAc and washed with H_2O and brine. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to yield a

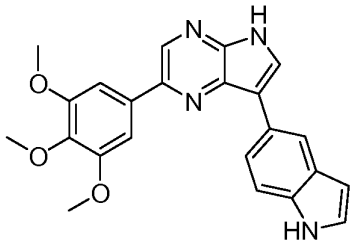
residue that was triturated with hexanes to yield the title compound (1.6 g, 94%) as a light yellow powder. ^{1}H NMR (DMSO-*d6*, 300MHz) δ 8.62 (d, *J* = 7.5 Hz, 2 H), 8.03 (s, 1 H), 8.00 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 2 H), 2.37 (s, 3H). HPLC retention time: 2.84 minutes. MS ESI (m/z): 478.0/480.0 $(M+H)^+$, calc. 477.

Preparation of 2-bromo-7-(1*H*-indol-5-yl)-5-tosyl-5*H*-pyrrolo[3,2-*b*]pyrazine (Intermediate AV)



[0318] To a stirred suspension of 2-bromo-7-iodo-5-tosyl-5*H*-pyrrolo[3,2-*b*]pyrazine [Intermediate **AU**] (0.25 g, 0.52 mmol) and 1*H*-indol-5-ylboronic acid (0.10 mg, 0.62 mmol) in CH_3CN (20 mL) was added 1 M Na_2CO_3 (20 mL) followed by bis(triphenylphosphine)-palladium(II) dichloride (60 mg, 0.086 mmol). The resulting mixture was stirred for 2 h at 60°C. The title compound was isolated as a yellow solid via filtration from the CH_3CN layer (0.23 g, 94%). HPLC retention time: 3.23 minutes. MS ESI (m/z): 467.2/469.2 $(M+H)^+$, calc. 466.

Preparation of 7-(1*H*-indol-5-yl)-2-(3,4,5-trimethoxyphenyl)-5*H*-pyrrolo[3,2-*b*]pyrazine (Compound AW)

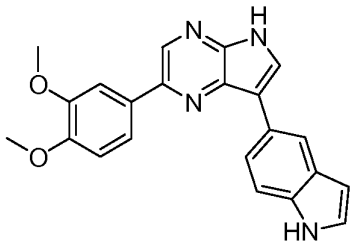


[0319] To a solution of 2-bromo-7-(1*H*-indol-5-yl)-5-tosyl-5*H*-pyrrolo[3,2-*b*]pyrazine [Intermediate **AV**] (65 mg, 0.14 mmol) in CH_3CN (1 mL) in a Personal Chemistry microwave reaction vial was added 3,4,5-trimethoxyphenylboronic acid (30 mg, 0.14 mmol), bis(triphenylphosphine)-palladium(II) dichloride (7.0 mg, 0.010 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 10 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered,

and concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL) and acetone (2 mL), and 2 M NaOH (1.5 mL) was added. The resulting mixture was stirred at 65°C for 30 min, after which it was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to give a residue which was purified by preparatory HPLC to give the title compound as a yellow solid. HPLC retention time: 2.25 minutes; MS ESI (m/z) 401.2 $(M+1)^+$, calc. 400.

Example 37

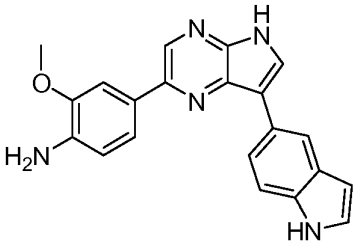
Preparation of 2-(3,4-dimethoxyphenyl)-7-(1*H*-indol-5-yl)-5*H*-pyrrolo[3,2-*b*]pyrazine (Compound AX)



[0320] Compound **AX** was prepared by a method analogous to that described in *Example 38* by substituting 3,4-dimethoxyboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate **AV**. HPLC retention time: 2.45 minutes. MS ESI (m/z): 371.2 $(M+H)^+$, calc. 370.

Example 38

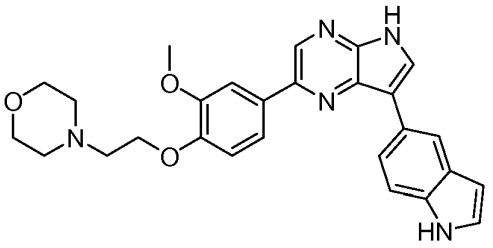
Preparation of 4-(7-(1*H*-indol-5-yl)-5*H*-pyrrolo[3,2-*b*]pyrazin-2-yl)-2-methoxyaniline (Compound AY)



Compound **AY** was prepared by a method analogous to that described in *Example 38* by substituting 4-amino-3-methoxyphenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with intermediate **AV**. HPLC retention time: 2.07 minutes. MS ESI (m/z): 356.4 $(M+H)^+$, calc. 355.

Example 39

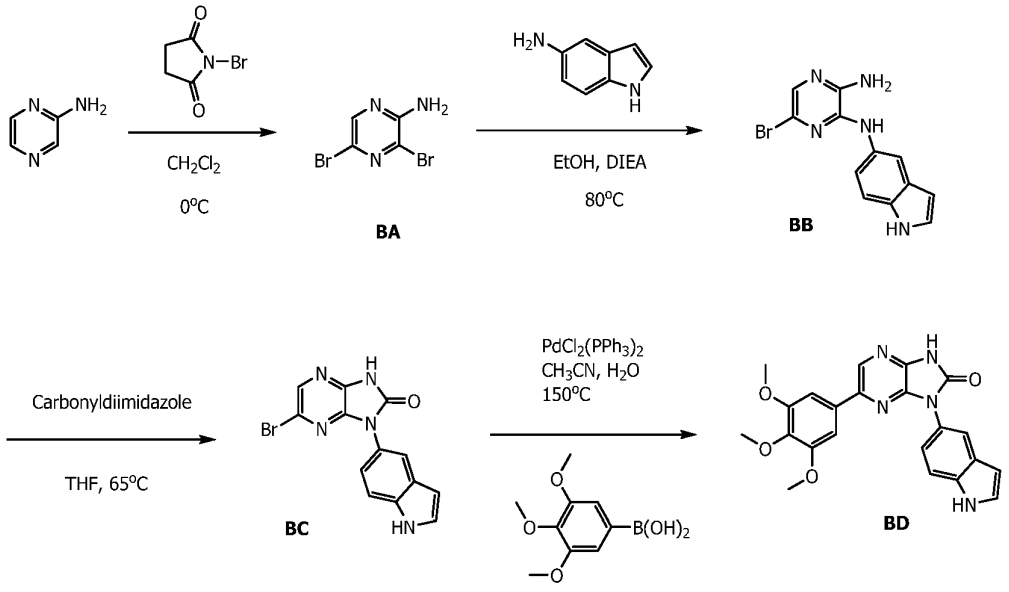
Preparation of 4-(2-(4-(7-(1*H*-indol-5-yl)-5*H*-pyrrolo[3,2-*b*]pyrazin-2-yl)-2-methoxyphenoxy)ethyl)morpholine (Compound AZ)



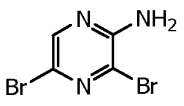
[0321] Compound **AZ** was prepared by a method analogous to that described in *Example 36* by substituting 4-(2-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine for 1-(2-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)piperazine and 2-bromo-7-(1*H*-indol-5-yl)-5-tosyl-5*H*-pyrrolo[3,2-*b*]pyrazine for intermediate **B**. HPLC retention time: 1.59 minutes. MS ESI (m/z): 470.4 $(M+H)^+$, calc. 469.

Example 40

Scheme 6

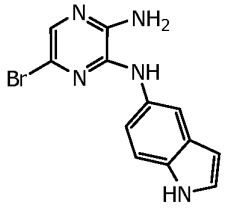


Preparation of 3,5-dibromopyrazin-2-amine (Intermediate BA)



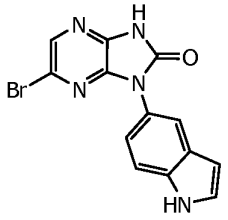
[0322] To a stirred solution of aminopyrazine (8.21 g, 86.4 mmol) in anhydrous methylene chloride (215 mL) cooled to 0°C was added *N*-bromosuccinimide (32.3 g, 181 mmol) in portions over a six hour period, during which time the temperature of the reaction was kept below 0°C. The resulting mixture was stored at 4°C overnight, after which it was stirred vigorously and quenched with H_2O (100 mL). The organic layer was separated, after which it was washed with saturated aqueous $NaHCO_3$, washed with brine, dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield a residue that was triturated with 20% EtOAc in hexanes to yield the title compound (10.3 g, 47%) as a yellow/brown powder. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.02 (s, 1H), 5.05 (bs, 2H); HPLC retention time: 1.99 minutes; MS ESI (m/z): 252.0/254.0/256.2 $(M+1)^+$, calc. 251.

Preparation of 6-bromo-N^2-(1*H*-indol-5-yl)pyrazine-2,3-diamine (Intermediate BB)



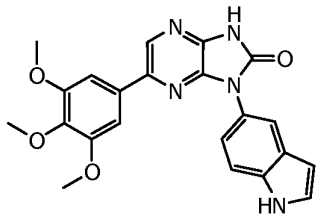
[0323] To a stirred suspension of 3,5-dibromopyrazin-2-amine (3.48 g, 13.7 mmol) and 1*H*-indol-5-amine (2.00 g, 15.0 mmol) in EtOH (3.5 mL) was added diisopropylethylamine [DIEA] (2.60 mL, 15.0 mmol). The resulting mixture was stirred for 48 hr at 80°C, after which it was partitioned between EtOAc and H_2O. The organic layer was separated, after which it was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to yield a residue that was purified via silica gel chromatography eluting with 1:1 EtOAc:hexanes to yield the title compound (1.75 g, 42%) as a red/brown solid. ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 10.98 (s, 1H), 8.22 (s, 1H), 7.83 (s, 1H), 7.31-7.28 (m, 3H), 7.19 (d, J = 8.7 Hz, 1H), 6.43 (s, 2H), 6.36 (s, 1H); HPLC retention time: 2.07 minutes; MS ESI (m/z): 304.2/306.2 $(M+1)^+$, calc. 303.

Preparation of 6-bromo-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (Intermediate BC)



[0324] To a solution of 6-bromo-N^2-(1*H*-indol-5-yl)pyrazine-2,3-diamine (0.450 g, 1.48 mmol) in THF (5 mL) was added carbonyldiimidazole (1.20 g, 7.40 mmol). The resulting mixture was heated at 65°C for 48 hr, after which it was concentrated *in vacuo* and partitioned between EtOAc and H_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a residue that was purified via silica gel chromatography eluting with EtOAc to yield the title compound (0.20 g, 41%). HPLC retention time: 2.07 minutes; MS ESI (m/z): 330.2/332.2 $(M+1)^+$, calc. 329.

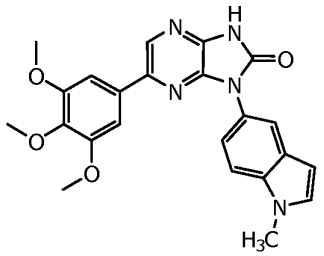
Preparation of 1-(1*H*-indol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (Compound BD)



[0325] To a solution of 6-bromo-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (27 mg, 0.08 mmol) in CH_3CN (1 mL) in a Personal Chemistry microwave reaction vial was added 3,4,5-trimethoxyphenylboronic acid (17 mg, 0.08 mmol), bis(triphenylphosphine)-palladium(II) dichloride (6.0 mg, 0.008 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 10 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue was purified by preparatory HPLC to yield the title compound (6.5 mg, 19%). ^1H NMR (DMSO-*d6*, 300 MHz): δ 12.18 (s, 1H), 11.28 (s, 1H), 8.57 (s, 1H), 7.83 (d, J = 1.8 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.42 (m, 1H), 7.37 (dd, J = 1.8, 8.4 Hz, 1H), 7.20 (s, 2H), 6.51 (m, 1H), 3.78 (s, 6H), 3.66 (s, 3H); HPLC retention time: 2.30 minutes; MS ESI (m/z): 418.4 $(M+1)^+$, calc. 417.

Example 41

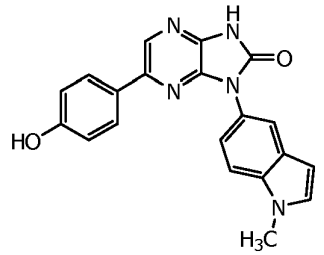
Preparation of 1-(1-methyl-1*H*-indol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (Compound BE)



[0326] Compound BE was prepared by a method analogous to that described in *Example 1* by substituting 1-methyl-1*H*-indol-5-amine for 1*H*-indol-5-amine in the reaction with Intermediate BA. 4.0 mg recovered. ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 12.22 (s, 1H), 8.57 (s, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.45 (d, J = 1.8 Hz), 7.41 (m, 2H), 7.20 (s, 2H), 6.50 (d, *J* = 3.0 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 6H), 3.66 (s, 3H); HPLC retention time: 2.50 minutes. MS ESI (m/z): 432.4 $(M+H)^+$, calc. 431.

Example 42

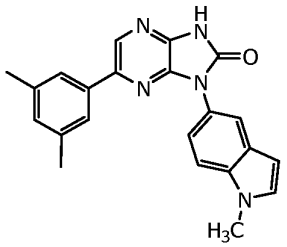
Preparation of 6-(4-hydroxyphenyl)-1-(1-methyl-1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (Compound BF)



[0327] Compound BE was prepared by a method analogous to that described in *Example 1* by substituting 1-methyl-1*H*-indol-5-amine for 1*H*-indol-5-amine in the reaction with Intermediate BA to prepare 6-bromo-1-(1-methyl-1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one. In a procedure similar to that used to synthesize Compound D, 4-hydroxyphenylboronic acid was substituted for 3,4,5-trimethoxyphenylboronic acid and 6-bromo-1-(1-methyl-1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one was substituted for 6-bromo-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one to obtain the title compound. 2.2 mg recovered. HPLC retention time: 2.18 minutes. MS ESI (m/z): 358.2 $(M+H)^+$, calc.357.

Example 43

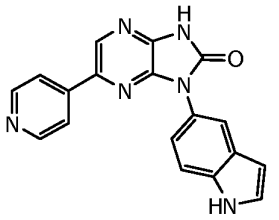
Preparation of 6-(3,5-dimethylphenyl)-1-(1-methyl-1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (Compound BG)



[0328] Compound BG was prepared by a method analogous to that described in *Example 3* by substituting 3,5-dimethylphenylboronic acid for 4-hydroxyphenylboronic acid in the reaction with 6-bromo-1-(1-methyl-1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one. 1.6 mg recovered. HPLC retention time: 3.04 minutes. MS ESI (m/z): 370.2 $(M+H)^+$, calc. 369.

Example 44

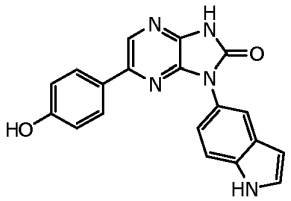
Preparation of 1-(1*H*-indol-5-yl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (Compound BH)



[0329] Compound BH was prepared by a method analogous to that described in *Example 1* by substituting pyridin-4-ylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with Compound BC. 1.6 mg recovered. HPLC retention time: 1.10 minutes. MS ESI (m/z): 329.4 $(M+H)^+$, calc. 328.

Example 45

Preparation of 6-(4-hydroxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (Compound BI)

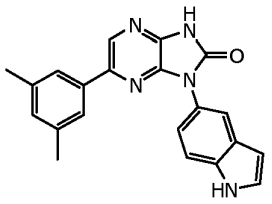


[0330] Compound BI was prepared by a method analogous to that described in *Example 1* by substituting by substituting 4-hydroxyphenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with Compound BC. 13.7 mg recovered. ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 12.07 (s, 1H), 11.30 (s, 1H), 9.61 (s, 1H), 8.38 (s, 1H), 7.69 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H),

7.44 (m, 1H), 7.26 (dd, J = 1.8, 8.7 Hz), 6.76 (dd, J = 2.4, 12.9 Hz), 6.52 (m, 1H); HPLC retention time: 1.99 minutes. MS ESI (m/z): 344.2 $(M+H)^+$, calc. 343.

Example 46

Preparation of 6-(3,5-dimethylphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (Compound BJ)

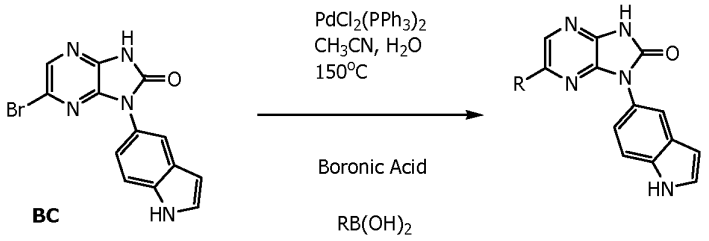


[0331] Compound BJ was prepared by a method analogous to that described in *Example 1* by substituting 3,5-dimethylphenylboronic acid for 3,4,5-trimethoxyphenylboronic acid in the reaction with Compound BC. 4.3 mg recovered. HPLC retention time: 2.80 minutes. MS ESI (m/z): 356.2 $(M+H)^+$, calc. 355.

[0332] Examples 47-119, shown in Table 3 below, were synthesized in parallel according to procedures given below in Schemes 7 and 8, using the reagents in Tables 1 and 2.

Examples 47-67

Scheme 7



Preparation of 1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one compounds in Table 1

[0333] To a solution of 6-bromo-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (27 mg, 0.08 mmol) in CH_3CN (1 mL) in a Personal Chemistry microwave reaction vial was added 3,4,5-trimethoxyphenylboronic acid (17 mg, 0.08 mmol), bis(triphenylphosphine)-palladium(II) dichloride (6.0 mg, 0.008 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 10 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue

was purified by preparatory HPLC to yield the title compounds (> 3 mg) in Table 1, isolated as amorphous solids.

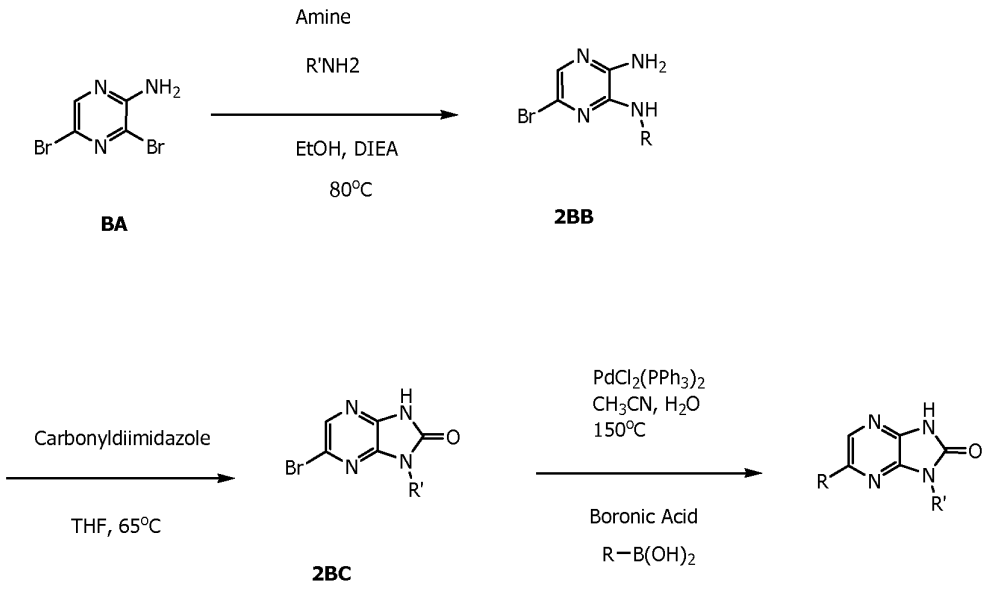
Table 1.

Example	Boronic Acid	Purified Compound Isolated
47	3,4-dimethoxyphenyl boronic acid	6-(3,4-dimethoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
48	3,5-dichlorophenyl boronic acid	6-(3,5-dichlorophenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
49	3-fluoro-4-methoxyphenyl boronic acid	6-(3-fluoro-4-methoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
50	3-amino-4-methoxyphenyl boronic acid	6-(3-amino-4-methoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
51	4-methoxy-3,5-dimethylphenyl boronic acid	1-(1*H*-indol-5-yl)-6-(4-methoxy-3,5-dimethylphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
52	4-morpholinophenyl boronic acid	1-(1*H*-indol-5-yl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
53	Indole-5-boronic acid	1,6-di(1H-indol-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one
54	3-hydroxyphenyl boronic acid	6-(3-hydroxyphenyl)-1-(1H-indol-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one
55	4-hydroxy-3-methoxyphenyl	6-(4-hydroxy-3-methoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
56	indole-6-boronic	1-(1*H*-indol-5-yl)-6-(1*H*-indol-6-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
57	3-methoxy-4-(2-morpholinoethoxy)phenyl boronic acid	1-(1*H*-indol-5-yl)-6-(3-methoxy-4-(2-morpholinoethoxy)phenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one

58	2,5-difluoro-4-hydroxyphenyl boronic acid	6-(2,5-difluoro-4-hydroxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
59	3,5-difluoro-4-hydroxyphenyl boronic acid	6-(3,5-difluoro-4-hydroxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
60	4-amino-3-methoxyphenyl boronic acid	6-(4-amino-3-methoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
61	3,5-difluorophenyl boronic acid	6-(3,5-difluorophenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
62	4-hydroxy-3,5-dimethoxyphenyl boronic acid	6-(4-hydroxy-3,5-dimethoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
63	2,3-dihydrobenzo[b][1,4]dioxin-6- boronic acid	6-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
64	4-hydroxy-3,5-dimethylphenyl boronic acid	6-(4-hydroxy-3,5-dimethylphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
65	3,5-dimethoxyphenyl boronic acid	6-(3,5-dimethoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
66	2-(4-methylpiperazin-1-yl)pyridin-4-boronic acid	1-(1*H*-indol-5-yl)-6-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
67	(3-methoxy-4-(2-(piperazin-1-yl)ethoxy)phenyl	1-(1H-indol-5-yl)-6-(3-methoxy-4-(2-(piperazin-1-yl)ethoxy)phenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one

Examples 68-118

Scheme 8



Preparation of Intermediates 2BB

[0334] To a stirred suspension of 3,5-dibromopyrazin-2-amine (3.48 g, 13.7 mmol) and the corresponding alkyl, aryl, or heteroaryl amine (15.0 mmol) in EtOH (3.5 mL) was added diisopropylethylamine [DIEA] (2.60 mL, 15.0 mmol). The resulting mixture was stirred for 48 hr at 80°C, after which it was partitioned between EtOAc and H_2O. The organic layer was separated, after which it was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to yield a residue that was purified by automated medium pressure silica gel chromatography eluting with 1:1 EtOAc:hexanes to yield the intermediates as amorphous solids.

Preparation of intermediates 2BC

[0335] Intermediates 2BB (0.450 g, 1.5 mmol) were dissolved in THF (5 mL) and treated with carbonyldiimidazole (1.20 g, 7.40 mmol). The resulting mixture was heated at 65°C for 48 hr, after which it was concentrated *in vacuo* and partitioned between EtOAc and H_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a residue that was purified via automated silica gel chromatography eluting with hexane/EtOAc to yield the intermediates 2BC as amorphous solids.

Preparation of 1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one compounds in Table 2

[0336] Individual solutions of intermediates 2BC (0.08 mmol) in CH_3CN (1 mL) in a Personal Chemistry microwave reaction vial was added the corresponding lboronic acid (0.08 mmol), bis(triphenylphosphine)-palladium(II) dichloride (6.0 mg, 0.008 mmol), and 1 M

Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 10 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue was purified by preparatory HPLC to yield the title compounds in Table 2 (>3 mg) as amorphous solids.

Table 2.

Example	Boronic Acid	Amine	Purified Compound Isolated
68	3,4,5-trimethoxyphenyl boronic acid	4-methoxy-aniline	1-(4-methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
69	3,4-dimethoxyphenyl boronic acid	4-methoxy-aniline	6-(3,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
70	4-hydroxyphenyl boronic acid	4-methoxy-aniline	6-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
71	pyridin-4-boronic acid boronic acid	4-methoxy-aniline	1-(4-methoxyphenyl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
72	3,4,5-trimethoxyphenyl boronic acid	2-methyl-5-amino-indole	1-(2-methyl-1*H*-indol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
73	3,5-dichlorophenyl boronic acid	2-methyl-5-amino-indole	6-(3,5-dichlorophenyl)-1-(2-methyl-1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
74	3,4,5-trimethoxyphenyl boronic acid	1-amino-cyclopentane	1-cyclopentyl-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
75	3,4-dimethoxyphenyl boronic acid	1-amino-cyclopentane	1-cyclopentyl-6-(3,4-dimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
76	4-hydroxyphenyl boronic acid	1-amino-cyclopentane	1-cyclopentyl-6-(4-hydroxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
77	pyridin-4-boronic acid	1-amino-cyclopentane	1-cyclopentyl-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one

Example	Boronic Acid	Amine	Purified Compound Isolated
78	3,4,5-trimethoxyphenyl boronic acid	Cyclopropanemethylamine	1-(cyclopropylmethyl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
79	3,4-dimethoxyphenyl boronic acid	Cyclopropanemethylamine	1-(cyclopropylmethyl)-6-(3,4-dimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
80	3,5-dichlorophenyl boronic acid	Cyclopropanemethylamine	1-(cyclopropylmethyl)-6-(3,5-dichlorophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
81	4-hydroxyphenyl boronic acid	Cyclopropanemethylamine	1-(cyclopropylmethyl)-6-(4-hydroxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
82	4-aminopyridine boronic acid	Cyclopropanemethylamine	1-(cyclopropylmethyl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
83	3,4,5-trimethoxyphenyl boronic acid	1H-Indazol-5-amine	1-(1*H*-indazol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
84	4-hydroxypheny boronic acid	2-methyl-5-amino-indole	6-(4-hydroxyphenyl)-1-(2-methyl-1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
85	pyridin-4-boronic acid boronic acid	2-methyl-5-amino-indole	1-(2-methyl-1*H*-indol-5-yl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
86	4-morpholinophenyl boronic acid	Cyclopropanemethylamine	1-(cyclopropylmethyl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
87	3,4-dimethoxyphenyl boronic acid	1H-Indazol-5-amine	6-(3,4-dimethoxyphenyl)-1-(1*H*-indazol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
88	4-aminopyridine boronic acid	1H-Indazol-5-amine	1-(1*H*-indazol-5-yl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
89	4-morpholinophenyl boronic acid	1H-Indazol-5-amine	1-(1*H*-indazol-5-yl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one

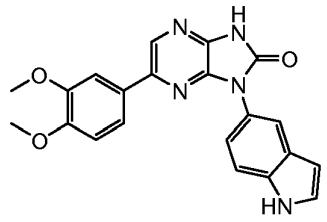
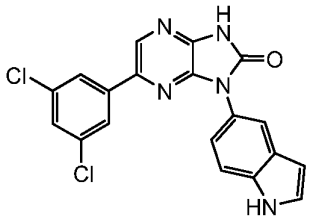
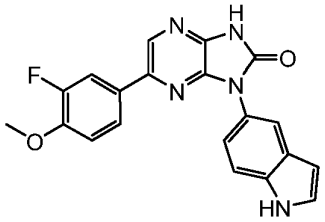
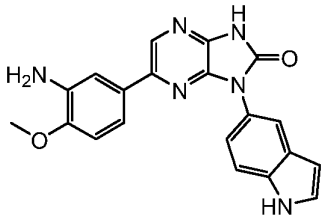
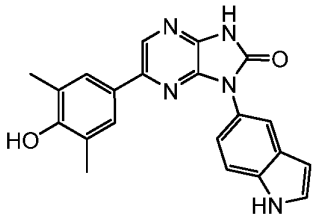
Example	Boronic Acid	Amine	Purified Compound Isolated
90	3,4,5-trimethoxyphenyl boronic acid	1H-Indazol-5-amine	1-(1*H*-indazol-6-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
91	3,4-dimethoxyphenyl boronic acid	1H-Indazol-5-amine	6-(3,4-dimethoxyphenyl)-1-(1*H*-indazol-6-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
92	4-hydroxyphenyl boronic acid	1H-Indazol-5-amine	6-(4-hydroxyphenyl)-1-(1*H*-indazol-6-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
93	4-aminopyridine boronic acid	1H-Indazol-5-amine	1-(1*H*-indazol-6-yl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
94	2,4,6-trimethoxyphenyl	1-amino-cyclopentane	1-cyclopentyl-6-(2,4,6-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
95	3,5-dimethylphenyl boronic acid	1H-Indazol-5-amine	6-(3,5-dimethylphenyl)-1-(1*H*-indazol-6-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
96	3,4,5-trimethoxyphenyl boronic acid	benzo[d]thiazol-5-amine	1-(benzo[*d*]thiazol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
97	4-hydroxyphenyl boronic acid	benzo[d]thiazol-5-amine	1-(benzo[*d*]thiazol-5-yl)-6-(4-hydroxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
98	4-aminopyridine boronic acid	benzo[d]thiazol-5-amine	1-(benzo[*d*]thiazol-5-yl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
99	3,5-dimethylphenyl boronic acid	benzo[d]thiazol-5-amine	1-(benzo[*d*]thiazol-5-yl)-6-(3,5-dimethylphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
100	4-morpholinophenyl boronic acid	benzo[d]thiazol-5-amine	1-(benzo[*d*]thiazol-5-yl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one

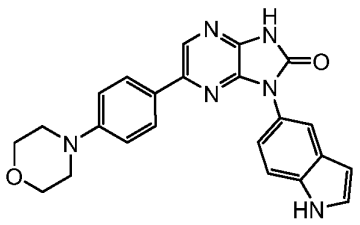
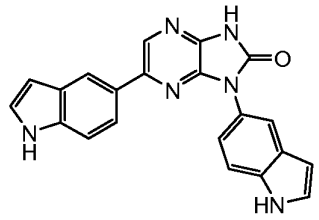
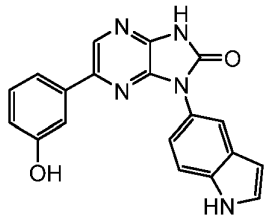
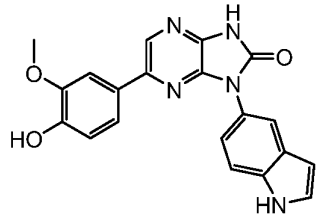
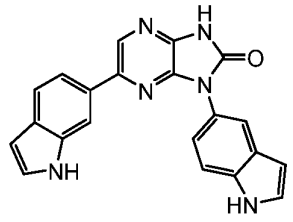
Example	Boronic Acid	Amine	Purified Compound Isolated
101	3,4,5-trimethoxyphenyl boronic acid	2,3-dihydro-1H-inden-1-amine	1-(2,3-dihydro-1*H*-inden-1-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
102	3,4,5-trimethoxyphenyl boronic acid	1H-benzo[d]imidazol-5-amine	1-(1*H*-benzo[*d*]imidazol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
103	3,4-dimethoxyphenyl boronic acid	1H-benzo[d]imidazol-5-amine	1-(1*H*-benzo[*d*]imidazol-5-yl)-6-(3,4-dimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
104	4-morpholinophenyl boronic acid	1H-benzo[d]imidazol-5-amine	1-(1*H*-benzo[*d*]imidazol-5-yl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
105	3,4,5-trimethoxyphenyl boronic acid	aniline	1-phenyl-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
106	3,4-dimethoxyphenyl boronic acid	aniline	6-(3,4-dimethoxyphenyl)-1-phenyl-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
107	3-methoxy-4-(2-morpholinoethoxy)phenyl boronic acid	Cyclopropanemethylamine	1-(cyclopropylmethyl)-6-(3-methoxy-4-(2-morpholinoethoxy)phenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
108	3-methoxy-4-(2-morpholinoethoxy)phenyl	1-amino-cyclopentane	1-cyclopentyl-6-(3-methoxy-4-(2-morpholinoethoxy)phenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
109	3,4,5-trimethoxyphenyl boronic acid	6-morpholinopyridin-3-amine	1-(6-morpholinopyridin-3-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
110	3,4,5-trimethoxyphenyl boronic acid	2,3-dihydro-1H-inden-2-amine	1-(2,3-dihydro-1*H*-inden-2-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one

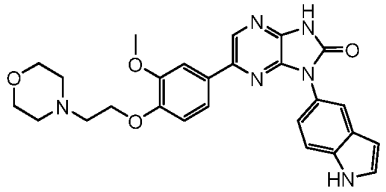
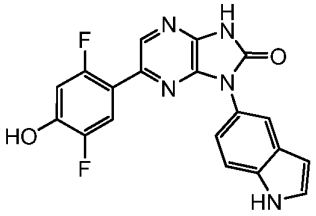
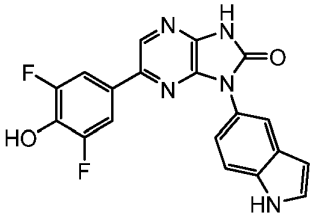
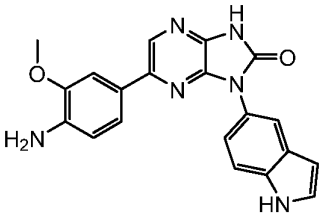
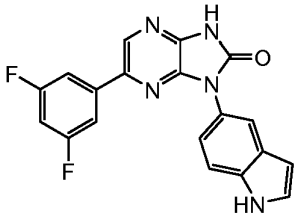
Example	Boronic Acid	Amine	Purified Compound Isolated
111	3,4-dimethoxyphenyl boronic acid	1H-pyrrolo[2,3-b]pyridin-5-amine	6-(3,4-dimethoxyphenyl)-1-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
112	3,4,5-trimethoxyphenyl boronic acid	1H-pyrrolo[2,3-b]pyridin-5-amine	1-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
113	3,4,5-trimethoxyphenyl boronic acid	1H-indol-6-amine	1-(1*H*-indol-6-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
114	3,4,5-trimethoxyphenyl boronic acid	4-aminophenol	1-(4-hydroxyphenyl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
115	3,4-dimethoxyphenyl boronic acid	4-aminophenol	6-(3,4-dimethoxyphenyl)-1-(4-hydroxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
116	4-morpholinophenyl boronic acid	4-aminophenol	1-(4-hydroxyphenyl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
117	6-aminopyridin-3-boronic acid	1-amino-cyclopentane	6-(6-aminopyridin-3-yl)-1-cyclopentyl-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one
118	4-amino-3-methoxyphenyl boronic acid	1-amino-cyclopentane	6-(4-amino-3-methoxyphenyl)-1-cyclopentyl-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one

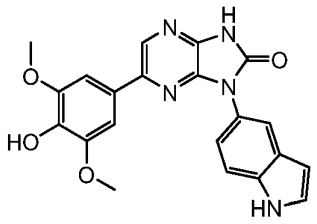
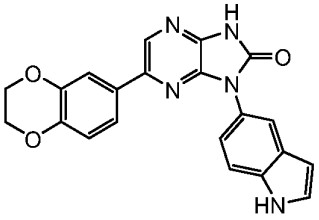
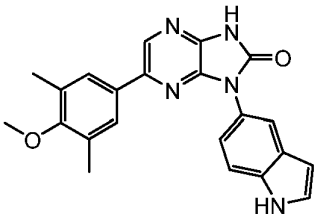
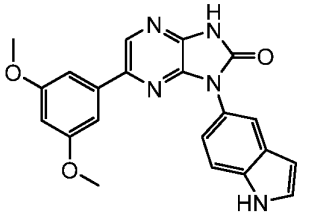
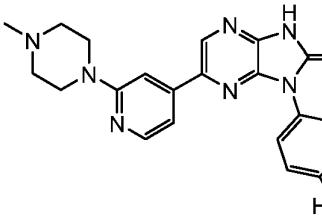
[0337] Examples 47-118 were were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 3.

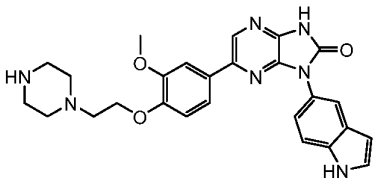
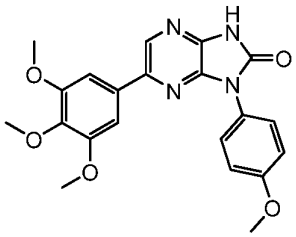
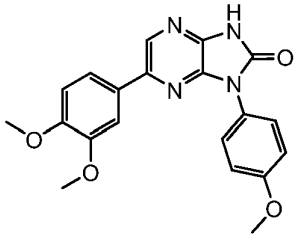
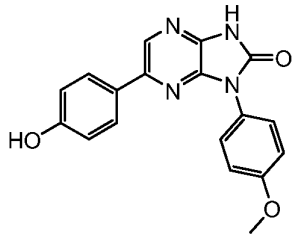
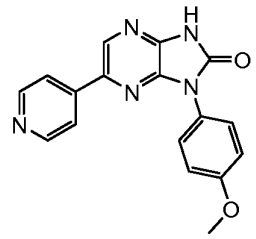
Table 3.

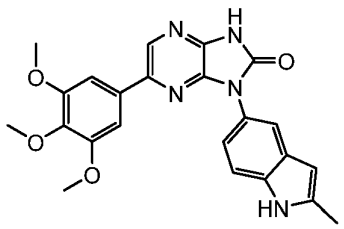
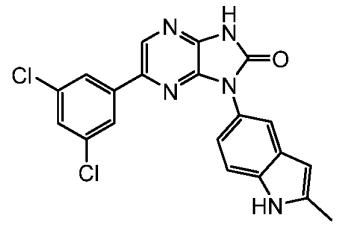
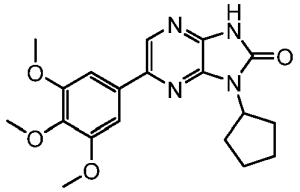
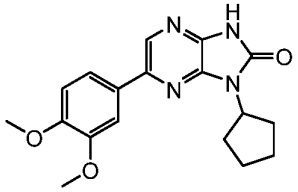
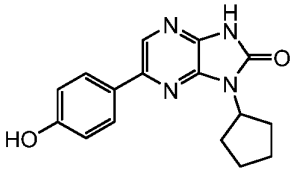
Example	Structure	IUPAC Name	MW
47		6-(3,4-dimethoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	387.13
48		6-(3,5-dichlorophenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	395.03
49		6-(3-fluoro-4-methoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	375.11
50		6-(3-amino-4-methoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	372.13
51		1-(1*H*-indol-5-yl)-6-(4-methoxy-3,5-dimethylphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	371.40

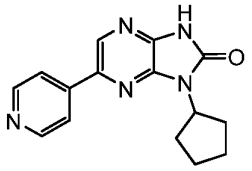
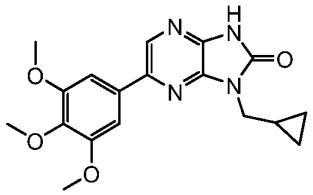
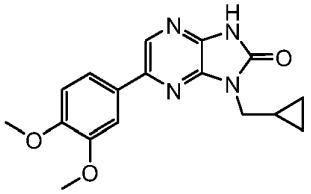
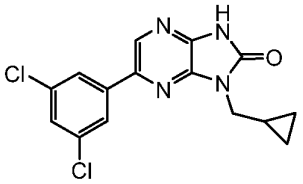
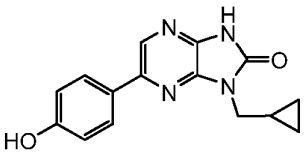
Example	Structure	IUPAC Name	MW
52		1-(1*H*-indol-5-yl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	412.45
53		1,6-di(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	366.39
54		6-(3-hydroxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	343.35
55		6-(4-hydroxy-3-methoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	373.37
56		1-(1*H*-indol-5-yl)-6-(1*H*-indol-6-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	366.39

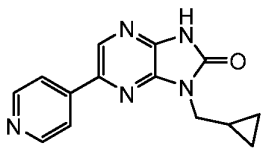
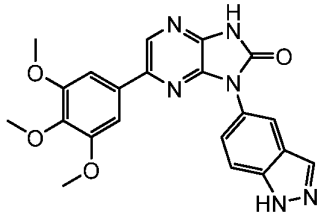
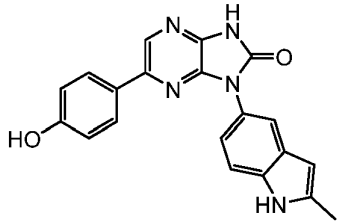
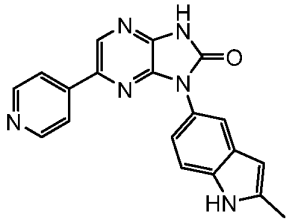
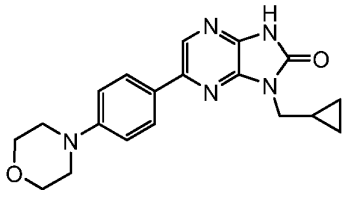
Example	Structure	IUPAC Name	MW
57		1-(1*H*-indol-5-yl)-6-(3-methoxy-4-(2-morpholinoethoxy)phenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	486.53
58		6-(2,5-difluoro-4-hydroxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	379.33
59		6-(3,5-difluoro-4-hydroxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	379.33
60		6-(4-amino-3-methoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	372.39
61		6-(3,5-difluorophenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	363.33

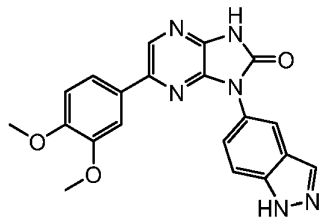
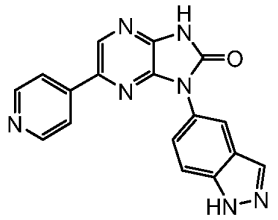
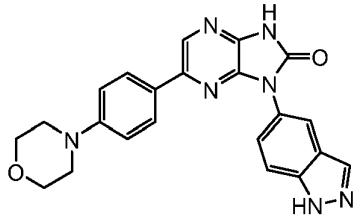
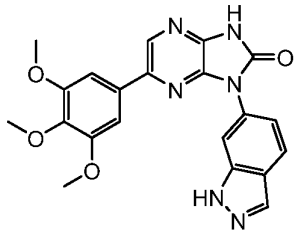
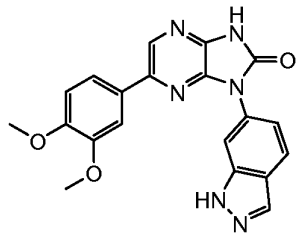
Example	Structure	IUPAC Name	MW
62		6-(4-hydroxy-3,5-dimethoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	403.40
63		6-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	385.39
64		6-(4-hydroxy-3,5-dimethylphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	385.43
65		6-(3,5-dimethoxyphenyl)-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	387.40
66		1-(1*H*-indol-5-yl)-6-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	426.50

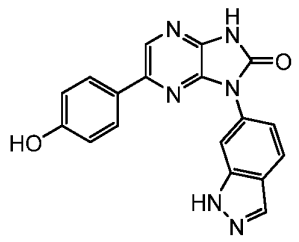
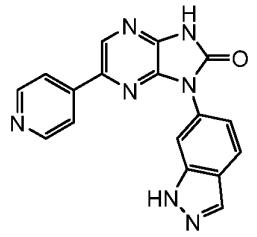
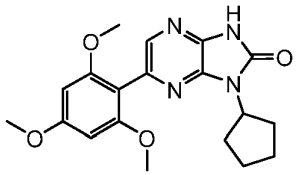
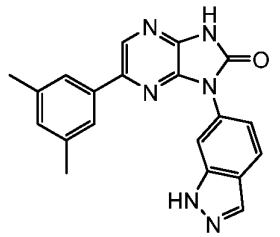
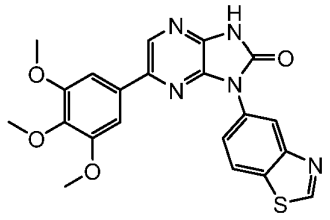
Example	Structure	IUPAC Name	MW
67		1-(1*H*-indol-5-yl)-6-(3-methoxy-4-(2-(piperazin-1-yl)ethoxy)phenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	485.55
68		1-(4-methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	408.42
69		6-(3,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	378.39
70		6-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	334.34
71		1-(4-methoxyphenyl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	319.33

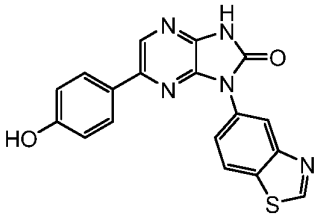
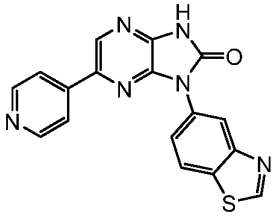
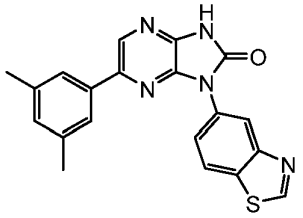
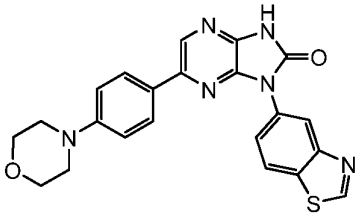
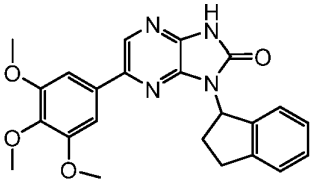
Example	Structure	IUPAC Name	MW
72		1-(2-methyl-1*H*-indol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	431.45
73		6-(3,5-dichlorophenyl)-1-(2-methyl-1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	410.27
74		1-cyclopentyl-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	**370.41**
75		1-cyclopentyl-6-(3,4-dimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	340.39
76		1-cyclopentyl-6-(4-hydroxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	296.33

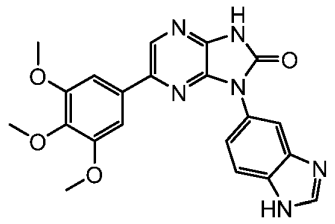
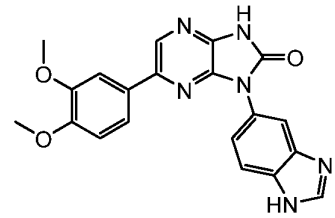
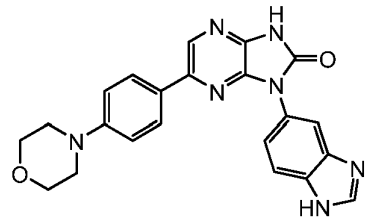
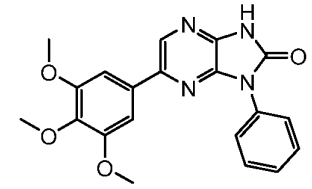
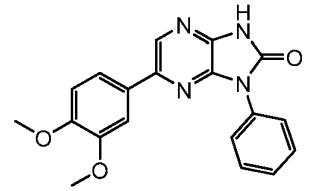
Example	Structure	IUPAC Name	MW
77		1-cyclopentyl-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	281.32
78		1-(cyclopropylmethyl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	**356.38**
79		1-(cyclopropylmethyl)-6-(3,4-dimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	326.36
80		1-(cyclopropylmethyl)-6-(3,5-dichlorophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	335.20
81		1-(cyclopropylmethyl)-6-(4-hydroxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	282.30

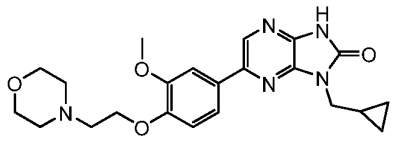
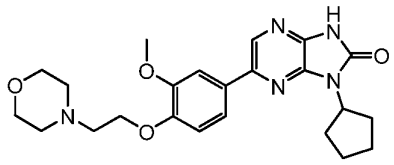
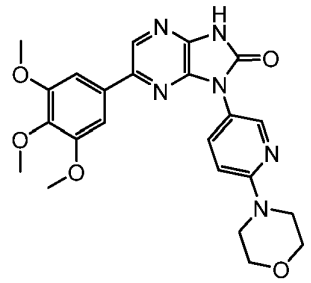
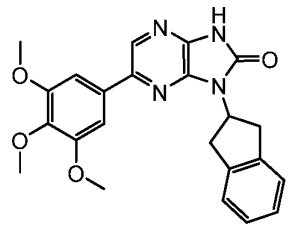
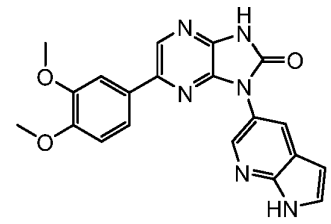
Example	Structure	IUPAC Name	MW
82		1-(cyclopropylmethyl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	267.29
83		1-(1*H*-indazol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	418.42
84		6-(4-hydroxyphenyl)-1-(2-methyl-1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	357.37
85		1-(2-methyl-1*H*-indol-5-yl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	342.36
86		1-(cyclopropylmethyl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	351.41

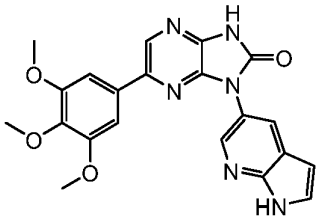
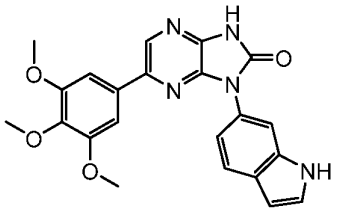
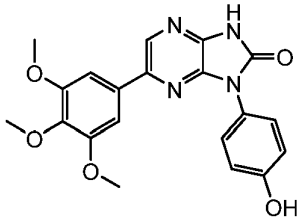
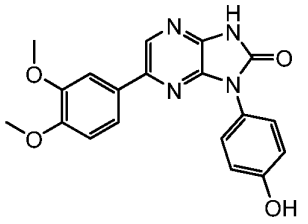
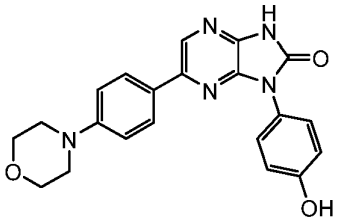
Example	Structure	IUPAC Name	MW
87		6-(3,4-dimethoxyphenyl)-1-(1*H*-indazol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	388.39
88		1-(1*H*-indazol-5-yl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	329.32
89		1-(1*H*-indazol-5-yl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	413.44
90		1-(1*H*-indazol-6-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	418.42
91		6-(3,4-dimethoxyphenyl)-1-(1*H*-indazol-6-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	388.39

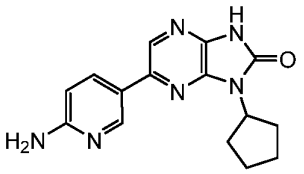
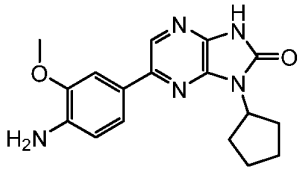
Example	Structure	IUPAC Name	MW
92		6-(4-hydroxyphenyl)-1-(1*H*-indazol-6-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	344.34
93		1-(1*H*-indazol-6-yl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	329.32
94		1-cyclopentyl-6-(2,4,6-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	370.41
95		6-(3,5-dimethylphenyl)-1-(1*H*-indazol-6-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	356.39
96		1-(benzo[*d*]thiazol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	435.46

Example	Structure	IUPAC Name	MW
97		1-(benzo[*d*]thiazol-5-yl)-6-(4-hydroxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	361.38
98		1-(benzo[*d*]thiazol-5-yl)-6-(pyridin-4-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	346.37
99		1-(benzo[*d*]thiazol-5-yl)-6-(3,5-dimethylphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	373.44
100		1-(benzo[*d*]thiazol-5-yl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	430.49
101		1-(2,3-dihydro-1*H*-inden-1-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	418.46

Example	Structure	IUPAC Name	MW
102		1-(1*H*-benzo[*d*]imidazol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	418.42
103		1-(1*H*-benzo[*d*]imidazol-5-yl)-6-(3,4-dimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	388.39
104		1-(1*H*-benzo[*d*]imidazol-5-yl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	413.44
105		1-phenyl-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	378.39
106		6-(3,4-dimethoxyphenyl)-1-phenyl-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	348.36

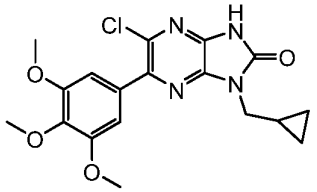
Example	Structure	IUPAC Name	MW
107		1-(cyclopropylmethyl)-6-(3-methoxy-4-(2-morpholinoethoxy)phenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	425.49
108		1-cyclopentyl-6-(3-methoxy-4-(2-morpholinoethoxy)phenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	439.52
109		1-(6-morpholinopyridin-3-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	464.48
110		1-(2,3-dihydro-1*H*-inden-2-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	418.46
111		6-(3,4-dimethoxyphenyl)-1-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	388.39

Example	Structure	IUPAC Name	MW
112		1-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	418.42
113		1-(1*H*-indol-6-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	418.42
114		1-(4-hydroxyphenyl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	394.50
115		6-(3,4-dimethoxyphenyl)-1-(4-hydroxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	364.50
116		1-(4-hydroxyphenyl)-6-(4-morpholinophenyl)-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	389.50

Example	Structure	IUPAC Name	MW
117		6-(6-aminopyridin-3-yl)-1-cyclopentyl-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	296.33
118		6-(4-amino-3-methoxyphenyl)-1-cyclopentyl-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one	325.37

Example 119

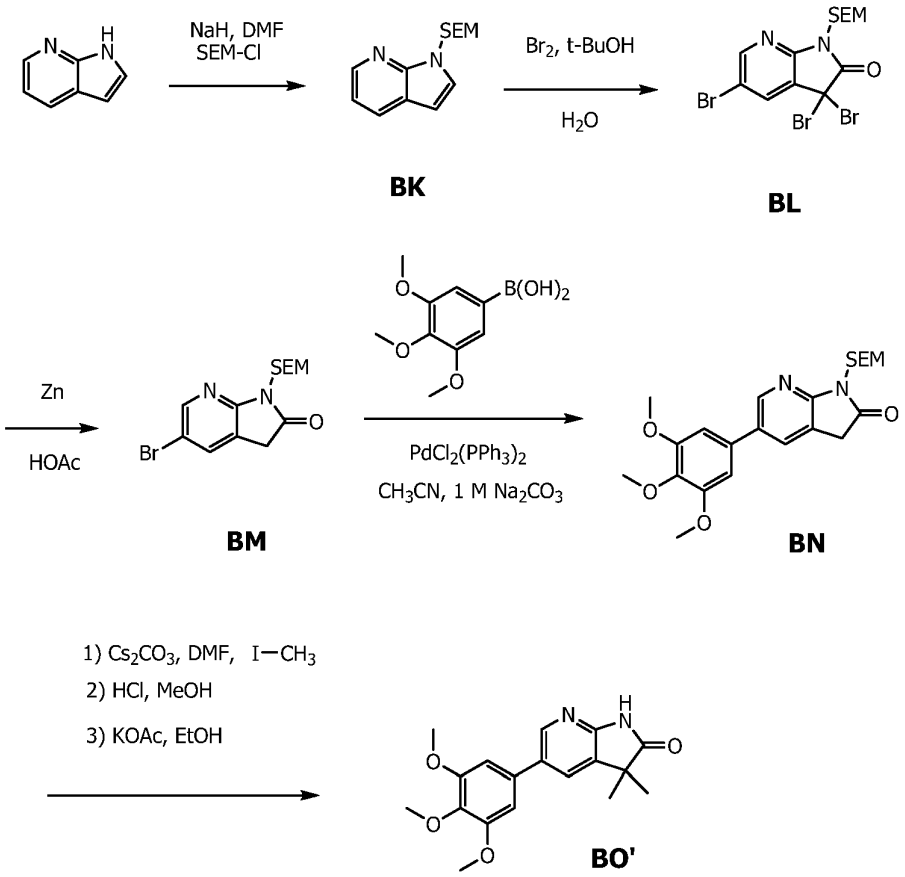
Preparation of 5-chloro-1-(cyclopropylmethyl)-6-(3,4,5-trimethoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one



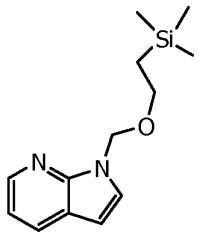
Example 119 was prepared by a method analogous to that described in *Examples 68-118* by substituting 6 chloro-**3**,5-dibromopyrazin-2-amine for 3,5-dibromopyrazin-2-amine in the reaction with aminomethylcyclopropane. MS ESI (m/z): 390.83 calc

Example 120

Scheme 9



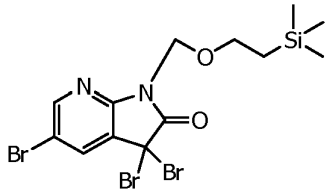
Preparation of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate BK)



[0338] To a stirred solution of 7-azaindole (1.18 g, 10.0 mmol) in anhydrous dimethylformamide (10 mL) cooled to 0°C was added NaH [60% dispersion in mineral oil] (0.480 g, 12.0 mmol) in portions over 15 min. The resulting mixture was allowed to stir for 1 hr at 0°C, after which (2-(chloromethoxy)ethyl)trimethylsilane [SEM-Cl] (2.12 mL, 12.0 mmol) was added over 15 min. The resulting mixture was stirred for 1 hr, after which it was quenched with H_2O (50 mL), and partioned between EtOAc and H_2O. The organic layer was separated,

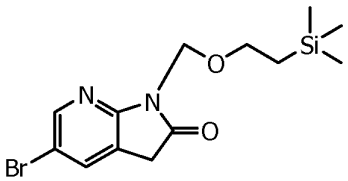
washed with brine, dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield a yellow oil (2.50 g, 100%). HPLC retention time: 2.66 minutes; MS ESI (m/z): 249.4 $(M+1)^+$, calc. 248.

Preparation of 3,3,5-tribromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (Compound BL)



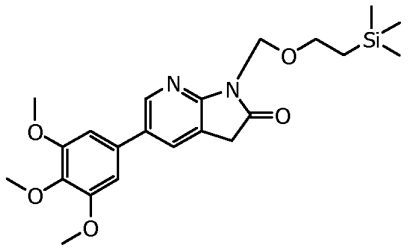
[0339] To a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.50 g, 10.0 mmol) in 1:1 *tert*-butanol/H_2O (140 mL) at room temperature was added bromine (6.40 mL, 126 mmol). After stirring for 3.5 hr at room temperature, an additional portion of bromine was added (6.40 mL, 126 mmol) and the resulting mixture was stirred for 18 hr. The resulting mixture was concentrated *in vacuo* to yield the title compound, which was used without any further purification. HPLC retention time: 2.97 minutes; MS ESI (m/z): 441.0/443.0/445.2 $(Fragment+1)^+$, calc. 498.

Preparation of 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (Compound BM)



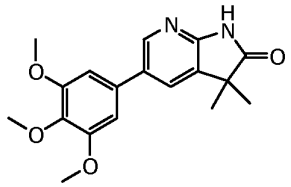
To a solution of 3,3,5-tribromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (4.98 g, 10.0 mmol) in AcOH (50 mL) was added zinc dust (1.28 g, 20.0 mmol). The resulting mixture was stirred at room temperature for 2 hr, after which it was filtered thru Celite and concentrated *in vacuo*. The resulting residue was purified via silica gel chromatography eluting with 1:1 Hexanes:EtOAc to yield the title compound as a yellow oil (0.85 g, 25% over three steps). HPLC retention time: 2.60 minutes; MS ESI (m/z): 287.2 $(Fragment+1)^+$, calc. 342.

Preparation of 5-(3,4,5-trimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (Compound BN)



[0340] To a solution of 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (0.85 g, 2.5 mmol) in CH_3CN (5 mL) was added 3,4,5-trimethoxyphenylboronic acid (525 mg, 2.5 mmol), bis(triphenylphosphine)-palladium(II) dichloride (250 mg, 0.35 mmol), and 1 M Na_2CO_3 (5 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 80°C for 2 hr. The reaction mixture was partitioned between EtOAc and H_2O, and the organic layer was separated, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 3:1 EtOAc:Hexanes to yield the title compound (640 mg, 60%). HPLC retention time: 2.51 minutes; MS ESI (m/z): 431.4 $(M+1)^+$, calc. 430.

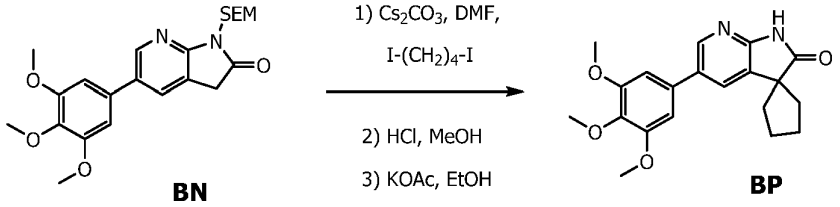
Preparation of 3,3-dimethyl-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (Compound BO)



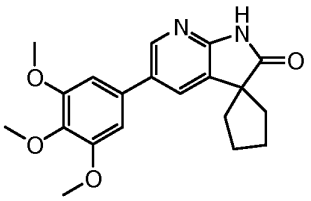
[0341] To a solution of 5-(3,4,5-trimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (43 mg, 0.10 mmol) in DMF (2 mL) was added cesium carbonate (0.17 g, 0.50 mmol) and methyl iodide (19 μL, 0.30 mmol). The resulting solution was stirred for 48 hr at room temperature, after which it was partitioned between EtOAc and H_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in 6 N HCl (10 mL) and MeOH (5 mL), and the resulting mixture was stirred at room temperature overnight, after which it was partitioned between EtOAc and H_2O. The organic layer was concentrated *in vacuo*, and the residue was dissolved in EtOH (2 mL). Potassium acetate (100 mg) was then added, and the reaction was stirred for 2 hr. The resulting solution was purified via preparatory HPLC to give the title compound (24 mg, 73%). ^1H NMR

($CDCl_3$, 300 MHz): δ 9.72 (s, 1H), 8.35 (d, J = 2.1 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H), 6.71 (s, 2H), 3.95 (s, 6H), 3.90 (s, 3H), 1.49 (s, 6H). HPLC retention time: 1.80 minutes; MS ESI (m/z): 329.4 $(M+1)^+$, calc. 328.

Example 121

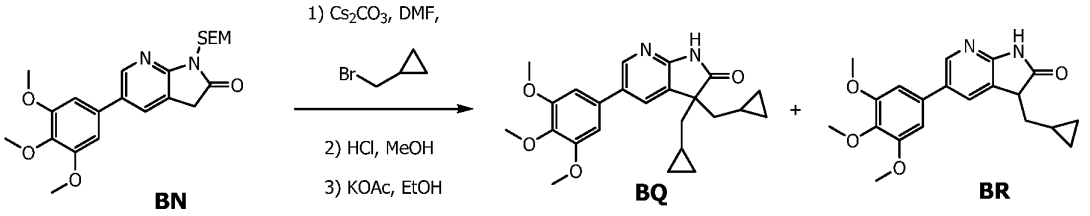


Preparation of 5'-(3,4,5-trimethoxyphenyl)spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (Compound BP)

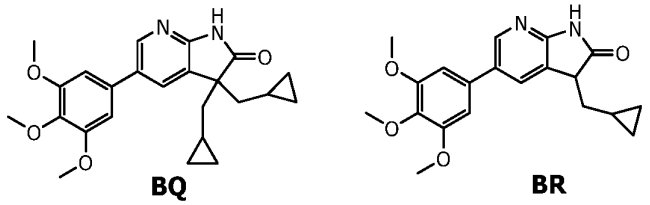


[0342] To a solution of 5-(3,4,5-trimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (Compound BN, 43 mg, 0.10 mmol) in DMF (2 mL) was added cesium carbonate (0.17 g, 0.50 mmol) and 1,4-diiodobutane (13 μL, 0.10 mmol). The resulting solution was stirred for 4 hr at room temperature, after which it was partitioned between EtOAc and H_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in 6 N HCl (10 mL) and MeOH (5 mL), and the resulting mixture was stirred at room temperature overnight, after which it was partitioned between EtOAc and H_2O. The organic layer was concentrated *in vacuo*, and the residue was dissolved in EtOH (2 mL). Potassium acetate (100 mg) was then added, and the reaction was stirred for 2 hr. The resulting solution was purified via preparatory HPLC to give the title compound (18 mg, 51%). ^1H NMR ($CDCl_3$, 300 MHz): δ 9.53 (s, 1H), 8.32 (d, J = 2.1 Hz, 1H), 7.56 (s, 1H), 6.69 (s, 2H), 3.95 (s, 6H), 3.90 (s, 3H), 2.28 (m, 2H), 2.24 (m, 2H), 1.97 (m, 4H). HPLC retention time: 2.00 minutes; MS ESI (m/z): 355.4 $(M+1)^+$, calc. 354.

Examples 122 and 123



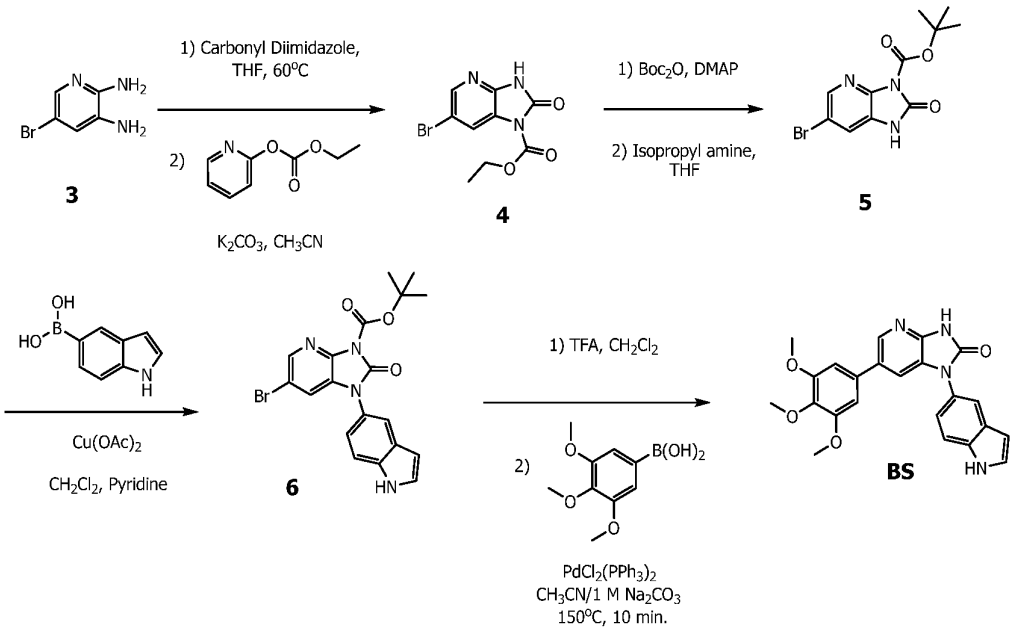
Preparation of 3,3-bis(cyclopropylmethyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (Example 122, Compound BQ) and 3-(cyclopropylmethyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (Example 123, Compound BR)



[0343] To a solution of 5-(3,4,5-trimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (43 mg, 0.10 mmol) in DMF (2 mL) was added cesium carbonate (0.17 g, 0.50 mmol), (bromomethyl)cyclopropane (10 μL, 0.10 mmol), and potassium iodide (83 mg, 0.50 mmol). The resulting solution was stirred for 4 hr at room temperature, after which it was partitioned between EtOAc and H_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in 6 N HCl (10 mL) and MeOH (5 mL), and the resulting mixture was stirred at room temperature overnight, after which it was partitioned between EtOAc and H_2O. The organic layer was concentrated *in vacuo*, and the residue was dissolved in EtOH (2 mL). Potassium acetate (100 mg) was then added, and the reaction was stirred for 2 hr. The resulting solution was purified via preparatory HPLC to give the Compound Q (11.4 mg) and Compound R (4.1 mg). Compound BQ: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.37 (d, J = 2.1 Hz, 1H), 7.71 (s, 1H), 6.72 (s, 2H), 3.96 (s, 6H), 3.91 (s, 3H), 2.04 (m, 2H), 1.69 (m, 2H), 1.26 (m, 2H), 0.88 (m, 2H), 0.40 (m, 2H), 0.29 (m, 2H), -0.07 (m, 2H). HPLC retention time: 2.49 minutes; MS ESI (m/z): 409.4 $(M+1)^+$, calc. 408. Compound BR: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.31 (s, 1H), 7.92 (s, 1H), 6.69 (s, 2H), 3.95 (s, 6H), 3.91 (s, 3H), 3.50 (m, 1H), 2.18 (m, 1H), 1.78 (m, 1H), 1.26 (m, 1H), 0.83 (m, 2H), 0.25 (m, 2H). HPLC retention time: 2.32 minutes; MS ESI (m/z): 355.0 $(M+1)^+$, calc. 354.

Example 124

Scheme 10



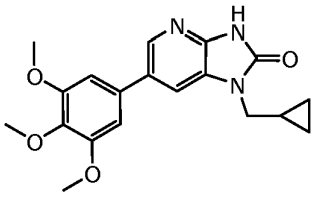
Preparation of 1-(1*H*-indol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (Compound BS)

[0344] Commercially available 5-bromopyridine-2,3-diamine **3** was converted to 6-bromo-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one via treatment with carbonyl diimidazole in THF at 60°C, which was then protected as the monoethoxy carbonyl derivative **4** in a fashion similar to that described in *J. Org. Chem.*, **1995**, 1565-1582. Intermediate **4** was subjected to an NOE analysis, and interactions between the 7-position hydrogen and the carbamate ethyl group were apparent, supporting the structure that is shown above. Following protection of the 3-position amine with a tert-butyl carboxylate group and deprotection of the ethyl carboxylate group using isopropyl amine, intermediate **6** was coupled to indole-5-boronic acid using copper acetate in a mixture of DCM/pyridine, after which it was deprotected using TFA/CH_2Cl_2. To the resulting 6-bromo-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one in CH_3CN (1 mL) in a microwave reaction vial was added 3,4,5-trimethoxyphenylboronic acid (30 mg, 0.14 mmol), bis(triphenylphosphine)-palladium(II) dichloride (7.0 mg, 0.010 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 10 min in a Personal Chemistry Optimizer. The resulting mixture was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered,

and stripped to give a residue that was purified via preparatory HPLC to give 1.8 mg of the title compound. HPLC retention time: 2.36 minutes; MS ESI (m/z): 417.4 $(M+1)^+$, calc. 416.

Example 125

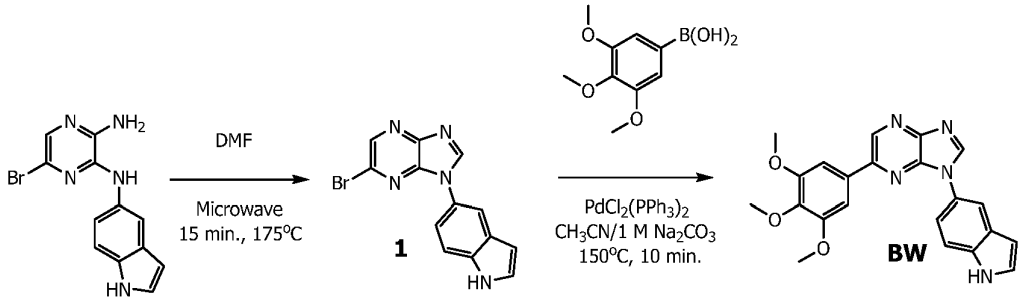
Preparation of 1-(cyclopropylmethyl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one



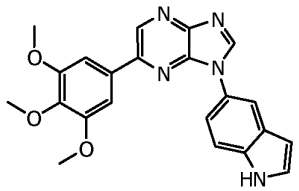
[0345] Intermediate 5 from *Example 124* was alkylated with (bromomethyl)cyclopropane using K_2CO_3 in acetone, after which it was deprotected using TFA/CH_2Cl_2. To the resulting 6-bromo-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one in CH_3CN (1 mL) in a microwave reaction vial was added 3,4,5-trimethoxyphenylboronic acid (30 mg, 0.14 mmol), bis(triphenylphosphine)-palladium(II) dichloride (7.0 mg, 0.010 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 10 min in a Personal Chemistry Optimizer. The resulting mixture was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to give a residue that was purified via preparatory HPLC to give 3.7 mg of the title compound. HPLC retention time: 1.90 minutes; MS ESI (m/z): 356.2 $(M+1)^+$, calc. 355.

Example 126

Scheme 11



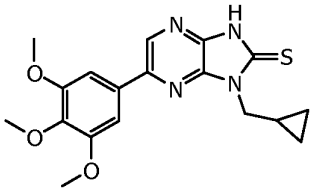
Preparation of 1-(1*H*-indol-5-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazine (Compound BW)



[0346] Following a method described in *Pteridines*, 2002, Vol. 13, 65-72, **Intermediate BB** was heated in anhydrous DMF at 175°C for 15 min. in a Personal Chemistry Optimizer. To the resulting 6-bromo-1-(1*H*-indol-5-yl)-1*H*-imidazo[4,5-*b*]pyrazine 1 in CH_3CN (1 mL) in a microwave reaction vial was added 3,4,5-trimethoxyphenylboronic acid (30 mg, 0.14 mmol), bis(triphenylphosphine)-palladium(II) dichloride (7.0 mg, 0.010 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 10 min in a Personal Chemistry Optimizer. The resulting mixture was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to give a residue that was purified via preparatory HPLC to give 4.7 mg of the title compound. HPLC retention time: 2.43 minutes; MS ESI (m/z): 402.8 $(M+1)^+$, calc. 401.

Example 127

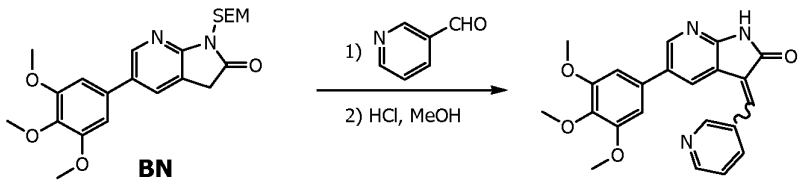
Preparation of 1-(cyclopropylmethyl)-6-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*b*]pyrazine-2(3*H*)-thione (Compound BX)



[0347] Compound BX was prepared by reacting *Example 78* with Lawesson's reagent in refluxing toluene. The resulting mixture was partitioned between EtOAc and 1 M $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to give a residue that was purified via preparatory HPLC to give 2.0 mg of the title compound. HPLC retention time: 2.29 minutes; MS ESI (m/z): 373.2 $(M+1)^+$, calc. 372.

Example 128

Scheme 12

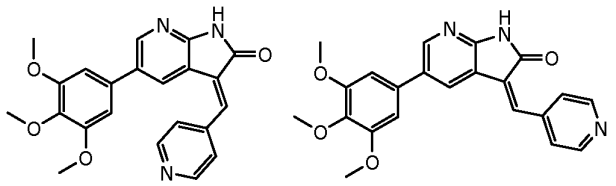


Preparation of 3-pyridin-3-ylmethylene-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

[0348] To a solution of 5-(3,4,5-trimethoxy-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (157 mg, 0.365 mmol) in toluene (2 mL) was added triethylamine (56 μl, 0.365 mmol), molecular sieves 4Å (100 mg), and 3-pyridinecarboxaldehyde (38 μl, 0.401 mmol). The resulting mixture was stirred overnight at room temperature, after which it was filtered and partitioned between DCM and H_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 40-70% EtOAc:Hexanes to yield the SEM-protected precursor as a mixture of cis and trans isomers (101 mg, 53%). 41 mg (0.079 mmol) of this material was dissolved in MeOH (1.5 ml), 6 N HCl (3 ml) was added, and the mixture was stirred for 3 hours at 45°C. The reaction was quenched with 1 N NaOH (15 ml), neutralized by the addition of saturated $NaHCO_3$ and extracted with DCM. Silica gel chromatography eluting with 0-5% MeOH:DCM yielded the title compound (22 mg, 72%) as a cis/trans-mixture. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.15 (d, J = 4.8 Hz, 1H), 9.11 (bs, 1H), 9.02 (d, J = 1.2 Hz, 1H), 8.98 (d, J = 1.1, 1H), 8.69 (dd, J = 0.9, 2.9 Hz, 1H), 8.66 (dd, J = 0.9, 2.8 Hz, 1H), 8.39 (d, J = 1.2 Hz, 1H), 8.37 (d, J = 1.2 Hz, 1H), 7.95 (m, 1H), 7.93 (s, 1H), 7.87 (d, J = 1.1 Hz, 1H), 7.44 (m, 1H), 6.75 (s, 2H), 6.59 (s, 2H), 3.97 (s, 6H), 3.91 (s, 3H), 3.90 (s, 6H), 3.86 (s, 3H).

Example 129

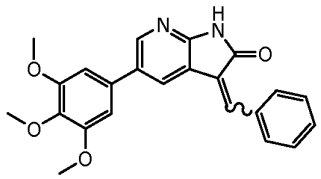
Preparation of (E)- and (Z)-3-pyridin-4-ylmethylene-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one



[0349] (E)- and (Z)-3-pyridin-4-ylmethylene-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one were prepared by a method analogous to that described in *Example 128* by substituting 3-pyridinecarboxaldehyde for 4-pyridinecarboxaldehyde in the reaction with Compound **BN**. The isomers were separated using silica gel chromatography eluting with 0-5% MeOH:DCM. Assignment of stereochemistry is tentatively based on the ^{1}H NMR spectra. ^{1}H NMR ($CDCl_3$, 300 MHz): E-isomer: δ 8.91 (s, 1H), 8.76 (d, (*J* = 3.6 Hz, 1H), 8.39 (d, *J* = 1.2 Hz, 1H), 8.02 (d, *J* = 3.7 Hz, 1H), 7.91 (d, *J* = 1.2 Hz, 1H), 7.52 (s, 1H), 6.74 (s, 2H), 3.96 (s, 6H), 3.91 (s, 3H). Z-isomer: δ 9.01 (s, 1H), 8.78 (d, (*J* = 3.5 Hz, 1H), 8.38 (d, *J* = 1.2 Hz, 1H), 7.87 (s, 1H), 7.81 (d, *J* = 1.2 Hz, 1H), 7.52 (d, *J* = 6.1 Hz, 1H), 6.56 (s, 2H), 3.89 (s, 6H), 3.88 (s, 3H).

Example 130

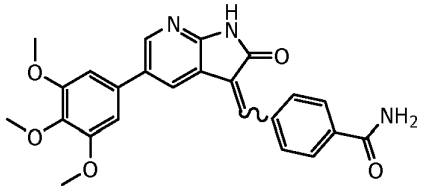
Preparation of 3-benzylidene-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one



[0350] 3-Benzylidene-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one was prepared by a method analogous to that described in *Example 128* by substituting 3-pyridinecarboxaldehyde for benzaldehyde in the reaction with Compound **BN**. 15 mg (33%) of the title compound were obtained.

Example 131

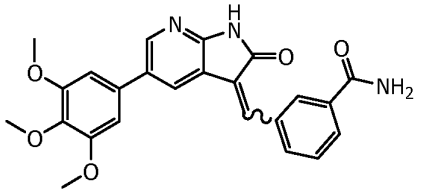
Preparatio of 4-[2-oxo-5-(3,4,5-trimethoxy-phenyl)-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl]-benzamide



[0351] 4-[2-Oxo-5-(3,4,5-trimethoxy-phenyl)-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl]-benzamideone was prepared by a method analogous to that described in *Example 128* by substituting 3-pyridinecarboxaldehyde for 4-formylbenzamide in the reaction with Compound **BN**. 25 mg (50%) of the title compound were obtained.

Example 132

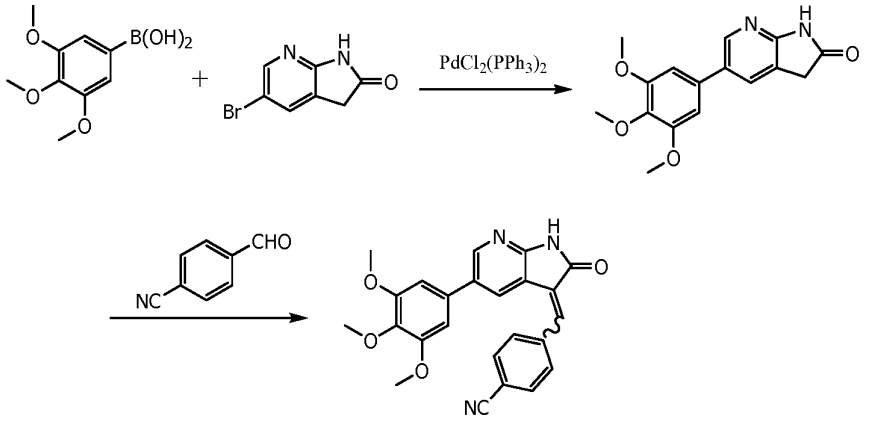
Preparatio of 3-[2-oxo-5-(3,4,5-trimethoxy-phenyl)-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl]-benzamide



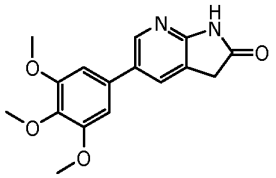
[0352] 3-[2-Oxo-5-(3,4,5-trimethoxy-phenyl)-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl]-benzamideone was prepared by a method analogous to that described in *Example 128* by substituting 3-pyridinecarboxaldehyde for 3-formylbenzamide in the reaction with Compound **BN**. 26 mg (52%) of the title compound were obtained.

Example 133

Scheme 13



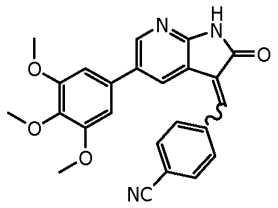
Preparation of 5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (Intermediate BY)



[0353] A mixture of 5-bromo-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (200mg, 0.939 mmol), 3,4,5-trimethoxyphenylboronic acid (239 mg, 1.127 mmol) and dichlorobis(triphenylphosphine)palladium (II) (33 mg, 0.047 mmol) in CH_3CN (5 ml) and 1 M Na_2CO_3 (5 ml) was heated in a microwave reactor for 10 min at 150°C. The reaction mixture was filtered, evaporated, partitioned between water and DCM and purified by silica gel chromatography with 0-10% MeOH:DCM to obtain 85 mg (30%) of compound #. ^{1}H NMR

($CDCl_3$/DMSO-d_6, 300 MHz): δ 10.19 (bs, 1H), 8.18 (d, *J* = 1.1 Hz, 1H), 7.54 (s, 1H), 6.57 (s, 2H), 3.80 (s, 6H), 3.75 (s, 3H), 3.47 (s, 2H).

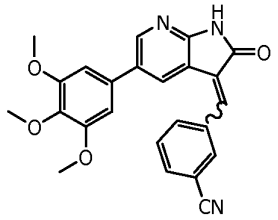
Preparation of 4-[2-oxo-5-(3,4,5-trimethoxy-phenyl)-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl]-benzonitrile



[0354] A mixture of 5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (Intermediate **BY**, 42 mg, 0.14 mmol), 4-cyanobenzaldehyde (22 mg, 0.168 mmol), triethylamine (22 µl, 0.168 mmol) and molecular sieves 4Å (100 mg) in toluene (2 ml) was reacted at 80°C for 1d. The mixture was partitioned between DCM and water, the aqueous phase extracted with DCM, combined organic phases dried, evaporated and purified by silica gel chromatography (0-5% MeOH:DCM) to obtain 31 mg (54%) of the title compound as a mixture of (E)- and (Z)-isomers.

Example 134

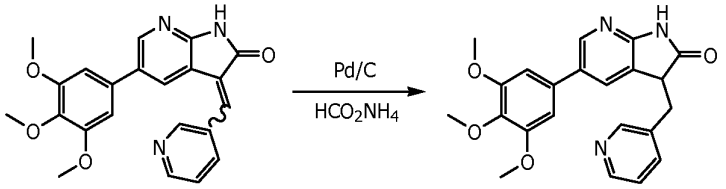
Preparation of 3-[2-oxo-5-(3,4,5-trimethoxy-phenyl)-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl]-benzonitrile



[0355] 3-[2-oxo-5-(3,4,5-trimethoxy-phenyl)-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl]-benzonitrile was prepared by a method analogous to that described in *Example 133* by substituting 4-cyanobenzaldehyde for 3-cyanobenzaldehyde in the reaction with Intermediate **BY**. 36 mg (62%) of the title compound were obtained as a mixture of cis- and trans-isomers.

Example 135

Scheme 14

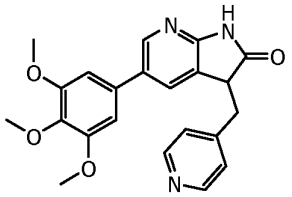


Preparation of 3-pyridin-3-ylmethyl-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

[0356] To a solution of 3-pyridin-4-ylmethylene-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (50 mg, 0.128 mmol) in MeOH (4 ml) was added ammonium formate (245 mg, 3.85 mmol) and Pd/C (10%, 30 mg). The mixture was stirred at room temperature for 3 hrs after which it was filtered, evaporated, and partitioned between water and DCM. The title compound (33 mg, 66%) was obtained after silica gel chromatography eluting with 0-10% MeOH:DCM. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.05 (s, 1H), 8.60 (d, J = 2.6 Hz, 1H), 8.45 (d, J = 1.1 Hz, 1H), 8.38 (d, J = 1.2 Hz, 1H), 7.62 (d, J = 4.7 Hz, 1H), 7.35 (dd, J = 2.9, 4.7 Hz, 1H), 6.53 (d, J = 1.2 Hz, 1H), 6.38 (s, 1H), 3.95 (m, 1H), 3.90 (m, 1H), 3.85 (s, 6H), 3.84 (s, 3H), 3.84 (m, 1H).

Example 136

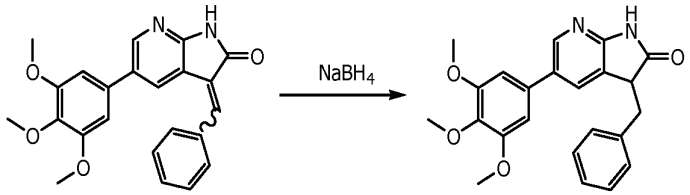
Preparation of 3-pyridin-4-ylmethyl-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one



[0357] 3-Pyridin-4-ylmethyl-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one was prepared by a method analogous to that described in *Example 135*. The title compound (14 mg, 61%) was obtained after silica gel chromatography eluting with 0-8% MeOH:DCM. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.52 (bs, 1H), 8.54 (d, J = 3.5 Hz, 1H), 8.32 (d, J = 1.1 Hz, 1H), 7.18 (d, J = 3.6 Hz, 1H), 7.12 (m, 1H), 6.54 (s, 1H), 3.91 (s, 6H), 3.89 (m, 1H), 3.88 (s, 3H), 3.54 (dd, J = 3.1, 8.3 Hz, 1H), 3.03 (dd, J = 5.6, 8.3 Hz, 1H).

Example 137

Scheme 15

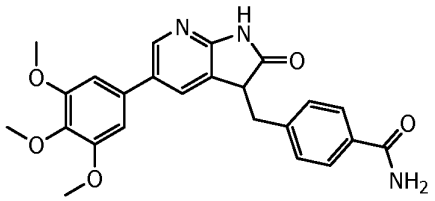


Preparation of 3-benzyl-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

[0358] To a solution of 3-benzylidene-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (41 mg, 0.106 mmol) in a mixture of MeOH (2 ml), THF (1 ml) and water (0.3 ml) was added sodium borohydride (40 mg, 1.06 mmol). The reaction was stirred at room temperature for 10 min after which it was quenched by the addition of 1 N HCl and partitioned between water and DCM. The residue was purified by preparatory HPLC to yield the title compound (5.2 mg, 13%).

Example 138

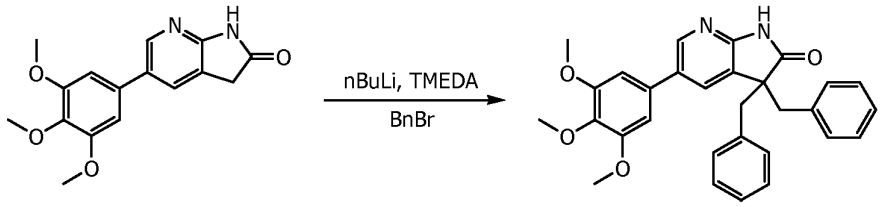
Preparation of 4-[2-oxo-5-(3,4,5-trimethoxy-phenyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-benzamide



[0359] 4-[2-Oxo-5-(3,4,5-trimethoxy-phenyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-benzamide was prepared from 4-[2-oxo-5-(3,4,5-trimethoxy-phenyl)-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl]-benzamideone by a method analogous to that described in *Example 137*. The title compound (12 mg, 54%) was obtained after silica gel chromatography eluting with 0-10% MeOH:DCM. ^{1}H NMR (DMSO-d6, 300 MHz): δ 11.06 (s, 1H), 8.34 (d, J = 1.5 Hz, 1H), 7.88 (s, 1H), 7.75 (d, J = 5.0 Hz, 2H), 7.41 (d, J = 0.5 Hz, 1H), 7.30 (s, 1H), 7.28 (d, J = 5.0 Hz, 2H), 6.74 (s, 2H), 4.03 (m, 1H), 3.82 (s, 6H), 3.67 (s, 3H), 3.44 (dd, J = 3.4, 8.2 Hz, 1H), 3.11 (dd, J = 4.6, 8.2 Hz, 1H).

Example 139

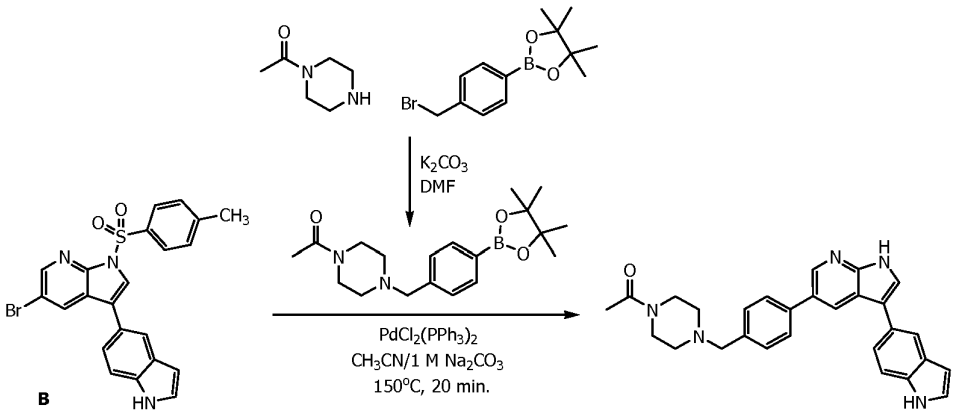
Preparation of 3,3-dibenzyl-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one



[0360] 5-(3,4,5-Trimethoxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (95 mg, 0.316 mmol) and TMEDA (96 µl, 0.623 mmol) were dissolved in anhydrous THF (4 ml) and cooled to -78°C. n-BuLi (1.6 M in hexanes, 415 µl, 0.664 mmol) was added dropwise. After completed addition stirring was continued for 1 hr at -78°C. Benzyl bromide (41.3 µl, 0.348 mmol) was added dropwise as a 10% solution in anh. THF. After completed addition the reaction was allowed to warm up to room temperature while stirring overnight. The reaction was quenched by the addition of MeOH, evaporated and partitioned between water and DCM. Silica gel chromatography eluting with 0-50% EtOAc:Hexanes yielded the title compound (47 mg, 38%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.83 (s, 1H), 8.18 (d, J = 1.2 Hz, 1H), 7.19 (d, J = 1.2 Hz, 1H), 7.14 (m, 6H), 6.99 (m, 4H), 6.61 (s, 2H), 3.96 (s, 6H), 3.90 (s, 3H), 3.30 (d, J = 8.0 Hz, 2H), 3.26 (d, J = 8.0 Hz, 2H).

Example 140

Preparation of 1-(4-{4-[3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzyl}-piperazin-1-yl)-ethanone

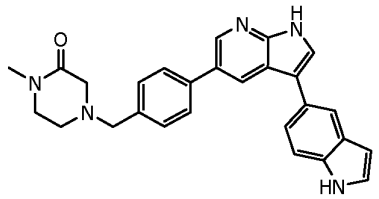


[0361] 2-(4-Bromomethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (100 mg, 0.337 mmol), N-acetylpiperazine (47 mg, 0.37 mmol) and K_2CO_3 (93 mg, 0.675 mmol) were combined

in DMF (2.5 ml) and stirred overnight at room temperature. The reaction was quenched by the addition of water, extracted with DCM and dried. The residue was taken up in CH_3CN (2 ml), Intermediate **B** (120 mg, 0.275 mmol) and dichlorobis(triphenylphosphine)palladium (II) (10 mg, 0.013 mmol) were added and the reaction was heated to 150°C in a microwave reactor for 20 min. The mixture was partitioned between water and DCM, the organic phase dried, evaporated and purified by silica gel chromatography using 0-5% MeOH:DCM. 53 mg (46%) of the title compound were obtained. MS ESI (m/z): 450.4 $(M+1)^+$, calc.449.

Example 141

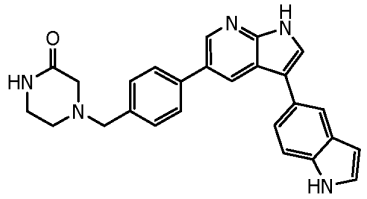
Preparation of 4-{4-[3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzyl}-1-methyl-piperazin-2-one



[0362] 4-{4-[3-(1H-Indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzyl}-1-methyl-piperazin-2-one was prepared by a method analogous to that described in *Example 140* by substituting N-acetylpiperazine for 1-methyl-piperazin-2-one. The title compound (14 mg, 28%) was obtained after silica gel chromatography eluting with 0-10% MeOH:DCM. MS ESI (m/z): 435.9 $(M+1)^+$, calc.435.

Example 142

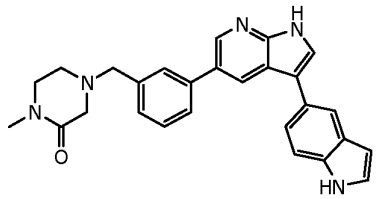
Preparation of 4-{4-[3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzyl}-piperazin-2-one



[0363] 4-{4-[3-(1H-Indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzyl}-piperazin-2-one was prepared by a method analogous to that described in *Example 140* by substituting N-acetylpiperazine for piperazin-2-one. The title compound (22 mg, 45%) was obtained after silica gel chromatography eluting with 0-10% MeOH:DCM. MS ESI (m/z): 422.2 $(M+1)^+$, calc. 421.

Example 143

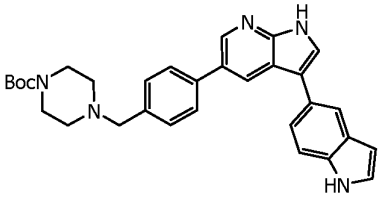
Preparation of 4-{3-[3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzyl}-1-methyl-piperazin-2-one



[0364] 4-{3-[3-(1H-Indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzyl}-1-methyl-piperazin-2-one was prepared by a method analogous to that described in *Example 140* by substituting N-acetylpiperazine for 1-methyl-piperazin-2-one and 2-(4-bromomethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane for 3-(bromomethyl)phenylboronic acid. The title compound (22 mg, 45%) was obtained after silica gel chromatography eluting with 0-10% MeOH:DCM. MS ESI (m/z): 436.4 $(M+1)^+$, calc. 435.

Example 144

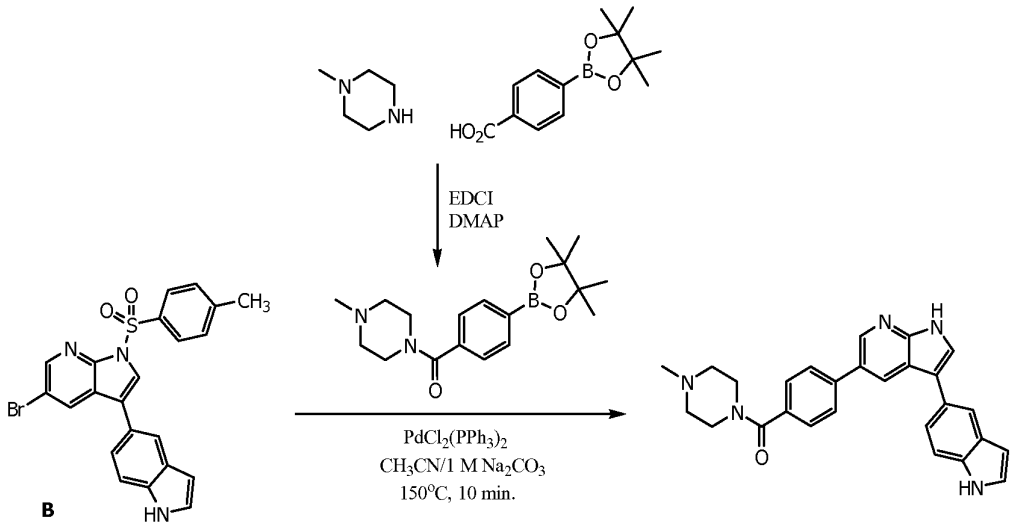
Preparation of 4-{4-[3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzyl}-piperazine-1-carboxylic acid tert-butyl ester



[0365] 4-{4-[3-(1H-Indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzyl}-piperazine-1-carboxylic acid tert-butyl ester was prepared by a method analogous to that described in *Example 140* by substituting N-acetylpiperazine for N-Boc-piperazine. The title compound (20 mg, 33%) was obtained after silica gel chromatography eluting with 0-3% MeOH:DCM. MS ESI (m/z): 508.2 $(M+1)^+$, calc. 507.

Example 145

Scheme 16

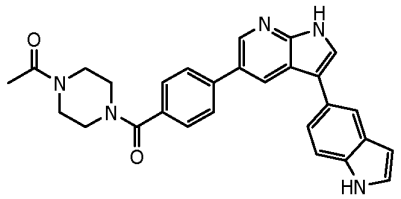


Preparation of {4-[3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone

[0366] 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (100 mg, 0.403 mmol), EDCI (97 mg, 0.504 mmol) and DMAP (catalytic amount) were combined in CH_3CN, stirred for 10 min and treated with N-methylpiperazine (54 µl, 0.484 mmol). The mixture was stirred overnight at room temperature. An aliquot of 650 µl was taken, combined with Intermediate **B** (50 mg, 0.107 mmol) and dichlorobis(triphenylphosphine)palladium (II) (10 mg, 0.013 mmol) and heated to 150°C in a microwave reactor for 20 min. The mixture was partitioned between water and DCM, the organic phase dried, evaporated and purified by silica gel chromatography using 0-6% MeOH:DCM. 13 mg (28%) of the title compound were obtained. ^{1}H NMR (DMSO-d6, 300 MHz): δ 11.88 (d, J = 1.5 Hz, 1H), 11.08 (s, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.45 (d, J = 1.8 Hz, 1H), 7.90 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.47 (m, 4H), 7.34 (t, J = 2.6 Hz, 1H), 6.47 (t, J = 2.4 Hz, 1H), 3.58 (bs, 4H), 2.3 (bs, 4H), 2.18 (s, 3H).

Example 146

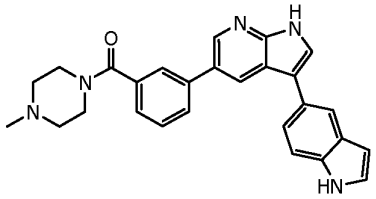
Preparation of 1-(4-{4-[3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzoyl}-piperazin-1-yl)-ethanone



[0367] 1-(4-{4-[3-(1H-Indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzoyl}-piperazin-1-yl)-ethanone was synthesized by a method analogous to that described in *Example 144* by substituting N-methylpiperazine for N-acetylpiperazine. The title compound (13 mg, 26%) was obtained after silica gel chromatography eluting with 0-5% MeOH:DCM. MS ESI (m/z): 464.2 $(M+1)^+$, calc. 463.

Example 147

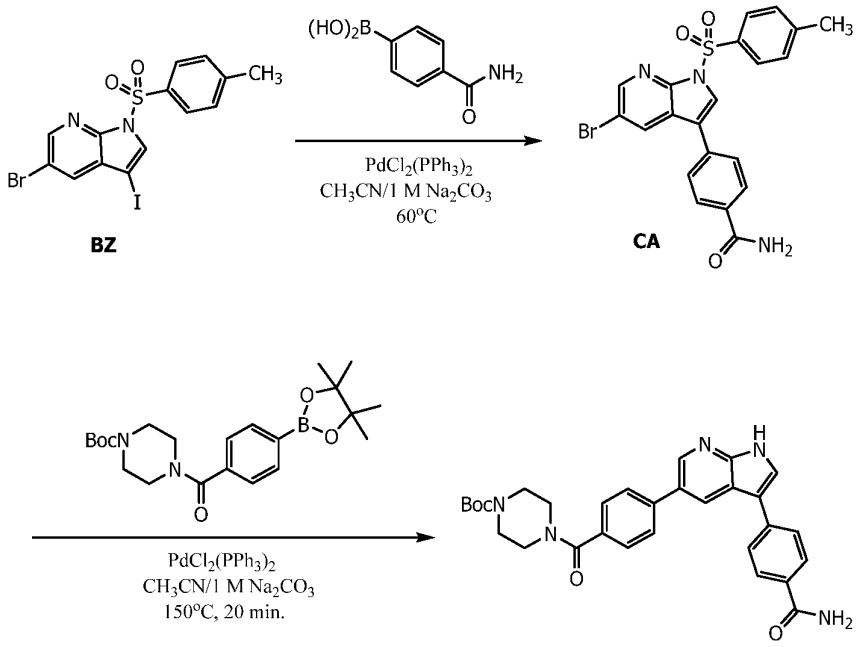
Preparation of {3-[3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



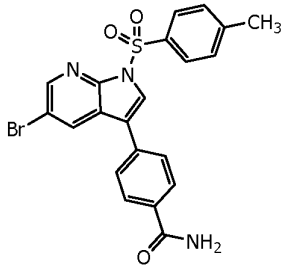
[0368] {3-[3-(1H-Indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone was synthesized by a method analogous to that described in *Example 144* by substituting 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid for 3-carboxyphenylboronic acid. The title compound (23 mg, 49%) was obtained after silica gel chromatography eluting with 5-10% MeOH:DCM. MS ESI (m/z): 436.4 $(M+1)^+$, calc. 435.

Example 148

Scheme 17

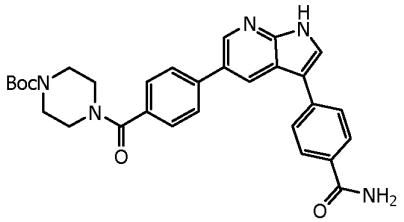


Preparation of 4-[5-bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzamide (Intermediate CA)



[0369] 5-Bromo-3-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (**Intermediate BZ**, 483 mg, 1.01 mmol), 4-aminocarbonylphenylboronic acid (196 mg, 1.22 mmol) and dichlorobis(triphenylphosphine)palladium (II) (71 mg, 0.1 mmol) were combined in CH_3CN (10 ml) and 1 M Na_2CO_3 (10 ml) and stirred at 60°C for 3 hrs. Water was added and the mixture was extracted with DCM and purified by silica gel chromatography using 0-30% EtOAc/Hexanes. The title compound was obtained in 79% yield (373 mg). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.51 (d, J = 1.2 Hz, 1H), 8.20 (d, J = 1.2 Hz, 1H), 8.11 (d, J = 5.1 Hz, 2H), 7.96 (s, 1H), 7.93 (d, J = 5.0 Hz, 2H), 7.64 (d, J = 5.1 Hz, 2H), 7.31 (d, J = 4.8 Hz, 2H), 6.1 (bs, 1H), 5.7 (bs, 1H), 2.39 (s, 3H).

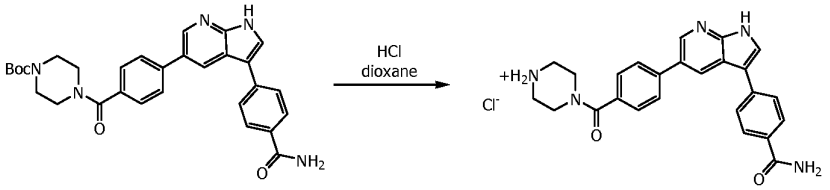
Preparation of 4-{4-[3-(4-carbamoyl-phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzoyl}-piperazine-1-carboxylic acid tert-butyl ester



[0370] 4-[5-Bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzamide (Intermediate **CA**, 200 mg, 0.425 mmol), 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoyl]-piperazine-1-carboxylic acid tert-butyl ester (212 mmg, 0.51 mmol) and dichlorobis(triphenylphosphine)palladium (II) (15 mg, 0. 021 mmol) were combined in CH_3CN (5 ml) and 1 M Na_2CO_3 (5 ml) and reacted in a microwave reactor at 150°C for 10 min. The mixture was filtered, water was added, extracted with EtOAc and purified by silica gel chromatography using 0-8% MeOH:DCM. The title compound was obtained in 46% yield (102 mg). ^{1}H NMR (DMSO-d6, 300 MHz): δ 12.2 (bs, 1H), 8.63 (d, J = 1.1 Hz, 1H), 8.54 (d, J = 1.1 Hz, 1H), 8.08 (s, 1H), 7.98 (bs, 1H), 7.96 (d, J = 5.1 Hz, 2H), 7.89 (m, 4H), 7.54 (d, J = 4.9 Hz, 2H), 7.32 (bs, 1H), 3.6 (bs, 2H), 3.4 (bs), 1.41 (s, 9H).

Example 149

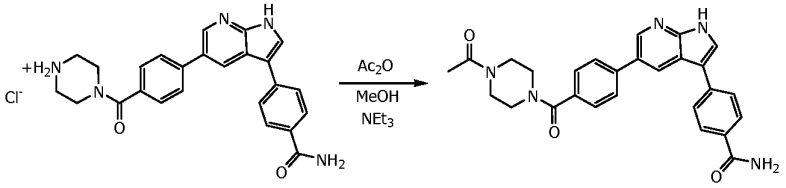
Preparation of 4-{5-[4-(piperazine-1-carbonyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide, hydrochloride salt



[0371] A solution of 4-{4-[3-(4-carbamoyl-phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzoyl}-piperazine-1-carboxylic acid tert-butyl ester (100 mg, 0.19 mmol) in MeOH (3 ml) was treated with 4 N HCl in dioxane (2.5 ml) and stirred at room temperature for 1 hr. The mixture was evaporated, taken up in MeOH and evaporated again. This was repeated twice to give 102 mg (116%) of the title compound. MS ESI (m/z): MS ESI (m/z): 426.4 $(M+1)^+$, calc. 425.

Example 150

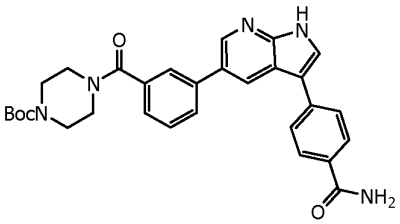
Preparation of 4-{5-[4-(4-acetyl-piperazine-1-carbonyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide



[0372] To a solution of 4-{5-[4-(piperazine-1-carbonyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide, hydrochloride salt (19 mg, 0.041 mmol) in MeOH (2 ml) was added triethylamine (400µl, 2.88 mmol) and acetic anhydride (100 µl, 1.06 mmol). The mixture was stirred for 1 hr at room temperature. EtOAc was added and washed with saturated aqu. $NaHCO_3$, water, brine and dried and evacuated. Purification on silica gel employing 0-10% MeOH:DCM provided 4.7 mg (25%) of the title compound. MS ESI (m/z): 468.3 $(M+1)^+$, calc. 467.

Example 151

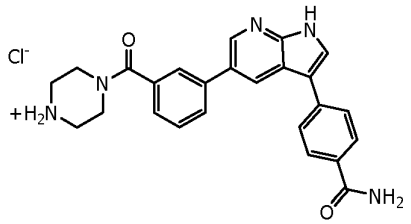
Preparation of 4-{3-[3-(4-carbamoyl-phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzoyl}-piperazine-1-carboxylic acid tert-butyl ester



[0373] 4-{3-[3-(4-Carbamoyl-phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzoyl}-piperazine-1-carboxylic acid tert-butyl ester was prepared by a method analogous to that described in *Example 148* by substituting 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoyl]-piperazine-1-carboxylic acid tert-butyl ester for 4-[3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoyl]-piperazine-1-carboxylic acid tert-butyl ester. The title compound (109 mg, 49%) was obtained after silica gel chromatography eluting with 0-8% MeOH:DCM. ^1H NMR (DMSO-d6, 300 MHz): δ 12.18 (bs, 1H), 8.61 (d, J = 1.2 Hz, 1H), 8.52 (d, J = 1.2 Hz, 1H), 8.07 (s, 1H), 7.96 (m, 3H), 7.89 (m, 3H), 7.80 (s, 1H), 7.57 (t, J = 4.6 Hz, 1H), 7.41 (d, J = 4.6 Hz, 1H), 7.32 (s, 1H), 3.63 (bs, 2H), 3.4 (bs, 2H), 1.40 (s, 9H).

Example 152

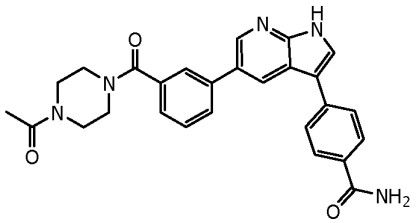
Preparation of 4-{5-[3-(piperazine-1-carbonyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide, hydrochloride salt



[0374] The hydrochloride salt of 4-{5-[3-(piperazine-1-carbonyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide was prepared by a method analogous to that described in *Example 149* by substituting 4-{4-[3-(4-carbamoyl-phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzoyl}-piperazine-1-carboxylic acid tert-butyl ester for 4-{3-[3-(4-carbamoyl-phenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzoyl}-piperazine-1-carboxylic acid tert-butyl ester. 105 mg (128%) of the title compound were obtained. ^{1}H NMR (DMSO-d6, 300 MHz): δ 12.32 (s, 1H), 9.52 (s, 2H), 8.66 (d, J = 1.8 Hz, 1H), 8.59 (d, J = 1.8 Hz, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.95 (m, 5H), 7.60 (t, J = 7.8 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.36 (bs, 1H), 3.6-4.0 (bs, 8H).

Example 153

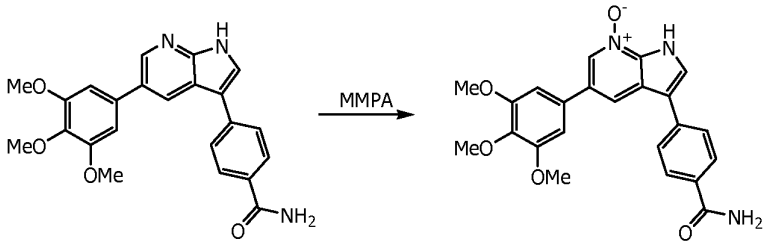
Preparation of 4-{5-[3-(4-acetyl-piperazine-1-carbonyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide



[0375] 4-{5-[3-(4-Acetyl-piperazine-1-carbonyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide was prepared by a method analogous to that described in *Example 150* by substituting 4-{5-[4-(piperazine-1-carbonyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide, hydrochloride salt for 4-{5-[3-(piperazine-1-carbonyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide, hydrochloride salt. 3.1 mg (14%) of the title compound were obtained. ^{1}H NMR (CD_3OD, 300 MHz): δ 8.56 (d, J = 1.2 Hz, 1H), 8.55 (d, J = 1.2 Hz, 1H), 7.99 (d, J = 4.2 Hz, 2H), 7.86 (m, 4H), 7.81 (d, J = 1.8 Hz, 1H), 7.62 (t, J = 4.6 Hz, 1H), 7.47 (dd, J = 0.7, 3.8 Hz, 1H), 3.5-3.9 (m, 8H), 2.14 (bd, 3H).

Example 154

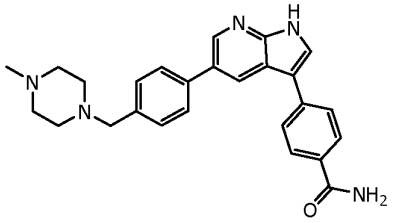
Preparation of 4-[7-oxy-5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzamide



[0376] 4-[5-(3,4,5-Trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzamide (50 mg, 0.124 mmol), magnesium monoperoxyphthalic acid (80%, 300 mg, 0.46 mmol) and acetic acid (10 drops were combined in EtOH (3 ml) and stirred at 50°C for 1 hr. After adding EtOAc the mixture was washed with saturated $NaHCO_3$, dried and purified by silica gel chromatography using 0-8% MeOH:DCM to provide 18 mg (33%) of the title compound. ^{1}H NMR (DMSO-d6, 300 MHz): δ 12.9 (bs, 1H), 8.62 (s, 1H), 8.14 (s, 1H), 8.0 (bs, 2H), 7.97 (d, J = 5.0 Hz, 2H), 7.89 (d, J = 5.0 Hz, 2H), 7.34 (bs, 1H), 7.04 (s, 2H), 3.89 (s, 6H), 3.70 (s, 3H).

Example 155

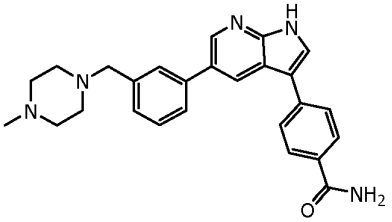
Preparation of 4-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide



[0377] 4-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide was prepared by a method analogous to that described in *Example 148* by substituting 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoyl]-piperazine-1-carboxylic acid tert-butyl ester for 1-methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine. The title compound (24 mg, 44%) was obtained by precipitation from DCM. ^{1}H NMR (DMSO-d6, 300 MHz): δ 12.1 (s, 1H), 8.57 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 1.2 Hz, 1H), 8.05 (d, J = 1.3 Hz, 1H), 7.98 (bs, 1H), 7.96 (d, J = 5.0 Hz, 2H), 7.88 (d, J = 5.1 Hz, 2H), 7.73 (d, J = 4.5 Hz, 2H), 7.40 (d, J = 4.5 Hz, 2H), 7.31 (bs,1H), 3.50 (s, 2H), 2.2-2.45 (bs, 8H), 2.15 (s, 3H).

Example 156

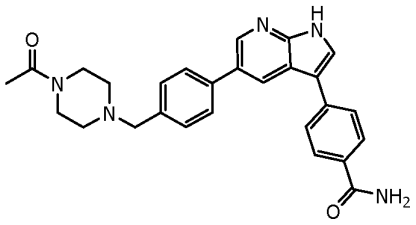
Preparation of 4-{5-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide



[0378] 4-{5-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide was prepared by a method analogous to that described in *Example 148* by substituting 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoyl]-piperazine-1-carboxylic acid tert-butyl ester for 1-methyl-4-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine. The title compound (8 mg, 15%) was obtained by precipitation from DCM. ^{1}H NMR (DMSO-d6, 300 MHz): δ 12.1 (s, 1H), 8.56 (d, *J* = 1.2 Hz, 1H), 8.46 (d, *J* = 1.2 Hz, 1H), 8.05 (d, *J* = 1.3 Hz, 1H), 7.96 (m, 3H), 7.88 (d, *J* = 5.1 Hz, 2H), 7.66 (m, 2H), 7.45 (m, 1H), 7.31 (m,2H), 3.55 (s, 2H), 2.2-2.45 (bs, 8H), 2.14 (s, 3H).

Example 157

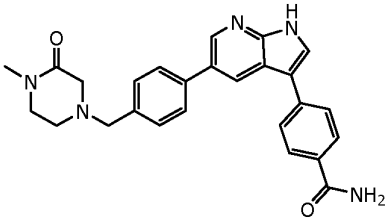
Preparation of 4-{5-[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide



[0379] 4-{5-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide was prepared by a method analogous to that described in *Example 140* by substituting Intermediate **B** with Intermediate **CA**. Purification by silica gel chromatography using 4-5% MeOH:DCM yielded the title compound (13 mg, 30%). MS ESI (m/z): 454.1 $(M+1)^+$, calc. 453.

Example 158

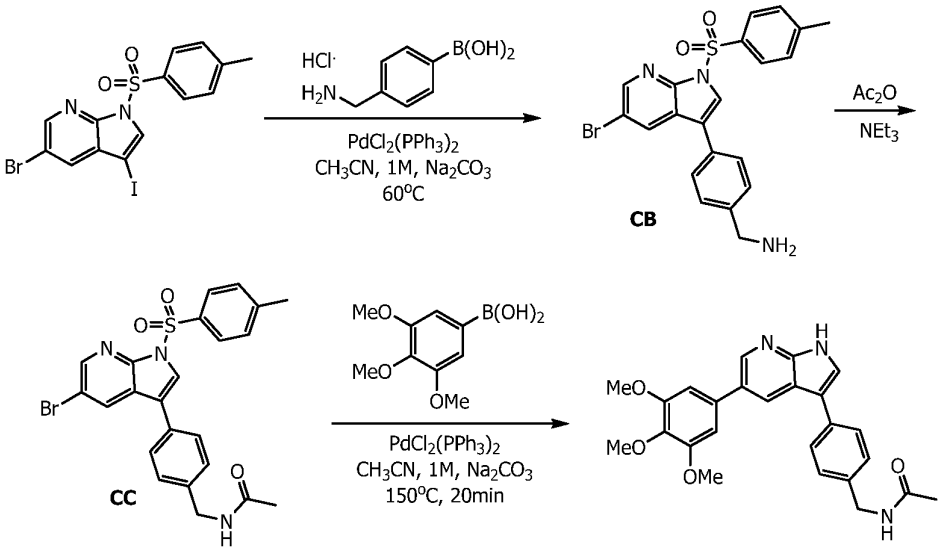
Preparation of 4-{5-[4-(4-methyl-3-oxo-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide



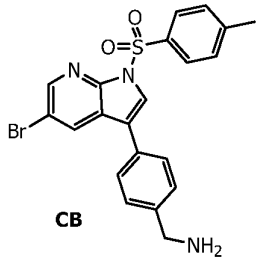
[0380] 4-{5-[4-(4-Methyl-3-oxo-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide was prepared by a method analogous to that described in *Example 140* by substituting Intermediate **B** with Intermediate **CA** and N-acetylpiperazine for 1-methyl-piperazin-2-one. Purification by silica gel chromatography using 4-5% MeOH:DCM yielded the title compound (4 mg, 10%). MS ESI (m/z): 440.3 $(M+1)^+$, calc. 439.

Example 159

Scheme 18



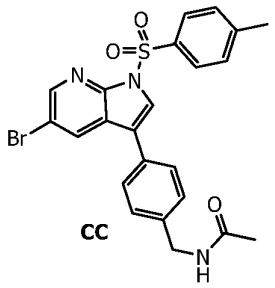
Preparation of 4-[5-bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzylamine (Intermediate CB)



[0381] 5-Bromo-3-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (200 mg, 0.419 mmol), 4-aminomethylphenylboronic acid hydrochloride (95 mg, 0.503 mmol) and dichlorobis(triphenylphosphine)palladium (II) (29 mg, 0.042 mmol) were combined in CH_3CN

(5 ml) and 1 M Na_2CO_3 (5 ml) and stirred at 60°C for 3 hrs. EtOAc was added, the organic phase was washed with water, dried and evaporated. to yield 136 mg (71%) of the title compound. MS ESI (m/z): 455.9/458.1 $(M+1)^+$, calc. 455/457.

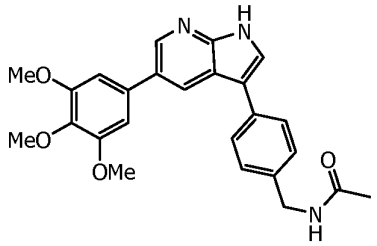
Preparation of N-{4-[5-bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzyl}-acetamide (Intermediate CC)



CC

[0382] 4-[5-Bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzylamine (Intermediate **CB**, 45 mg, 0.1 mmol) was combined with triethylamine (45 µl, 0.3 mmol) and acetic anhydride (11 µl, 0.11 mmol) in anh. DCM (2 ml). The mixture was stirred for 2 hrs, EtOAc, was added and washed with 0.5 N HCl, saturated $NaHCO_3$, water and brine. Evaporation yielded the title compound (48 mg, 96%). MS ESI (m/z): 498.1/500.1 $(M+1)^+$, calc. 497/499.

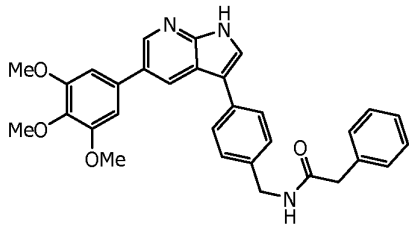
Preparation of N-{4-[5-(3,4,5-Trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzyl}-acetamide



[0383] N-{4-[5-Bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzyl}-acetamide (Intermediate **CC**, 24 mg, 0.048 mmol), 3,4,5-trimethoxyphenyl boronic acid (13 mg, 0.058 mmol) and dichlorobis(triphenylphosphine)palladium (II) (2 mg, 0.002 mmol) were combined in CH_3CN (1 ml) and 1 M Na_2CO_3 (2 ml) and heated in a microwave reactor at 150°C for 20 min. EtOAc was added, washed with water, dried and purified by silica gel chromatography eluting with 0-4% MeOH:DCM to give 11 mg (53%) of the title compound. MS ESI (m/z): 432.2 $(M+1)^+$, calc. 431.

Example 160

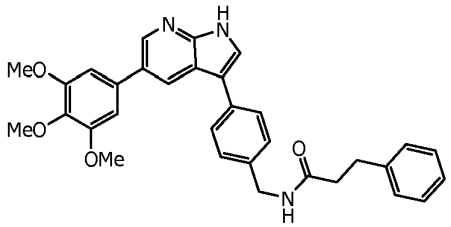
Preparation of 2-phenyl-N-{4-[5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzyl}-acetamide



[0384] 2-Phenyl-N-{4-[5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzyl}-acetamide was prepared by a method analogous to that described in *Example 159* by substituting acetic anhydride for phenacetyl chloride. Purification by silica gel chromatography using 0-4% MeOH:DCM yielded the title compound (9 mg, 38%). MS ESI (m/z): 508.3 $(M+1)^+$, calc.507.

Example 161

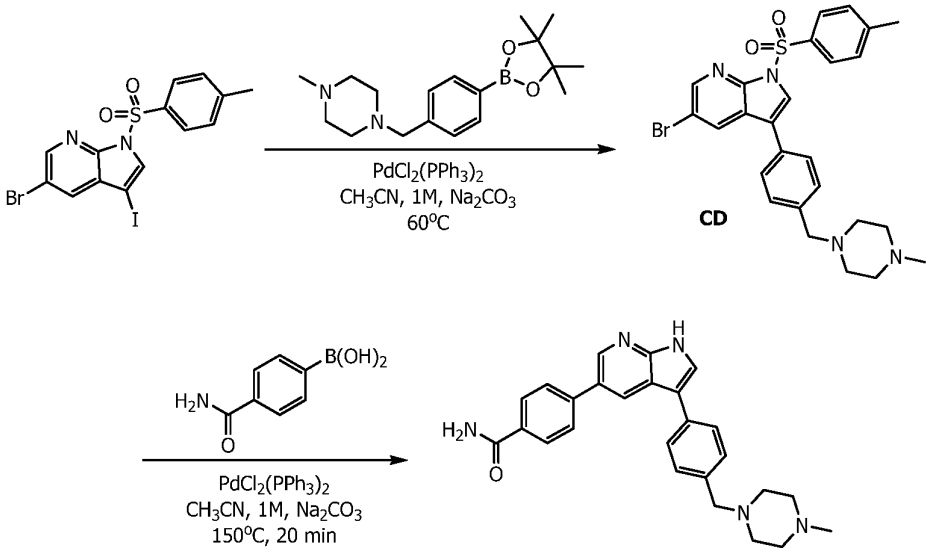
Preparation of 3-phenyl-N-{4-[5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzyl}-propionamide



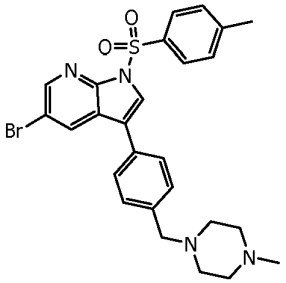
[0385] 3-Phenyl-N-{4-[5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzyl}-propionamide was prepared by a method analogous to that described in *Example 159* by substituting acetic anhydride for phenylpropionyl chloride. Purification by silica gel chromatography using 0-4% MeOH:DCM yielded the title compound (13 mg, 54%). MS ESI (m/z): 522.4 $(M+1)^+$, calc. 521.

Example 162

Scheme 19

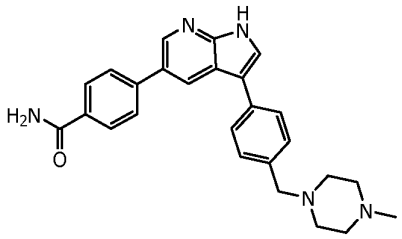


Preparation of 5-bromo-3-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate CD)



[0386] 5-Bromo-3-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (200 mg, 0.419 mmol), 1-methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine (160 mg, 0.503 mmol) and dichlorobis(triphenylphosphine)palladium (II) (30 mg, 0.042 mmol) were combined in CH_3CN (5 ml) and 1 M Na_2CO_3 (5 ml) and stirred at 60°C for 2 hrs. EtOAc was added and the organic phase was washed with water, dried and evaporated. Purification by silica gel chromatography using 0-20% MeOH:DCM yielded 235 mg (104%) of the title compound. MS ESI (m/z): 539.0/541.2 $(M+1)^+$, calc. 538/540.

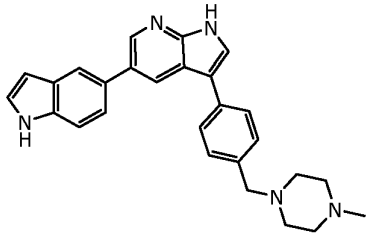
Preparation of 4-{3-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-benzamide



[0387] 5-Bromo-3-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate **CD**, 70 mg, 0.13 mmol), aminocarbonylphenylboronic acid (26 mg, 0.156 mmol) and dichlorobis(triphenylphosphine)palladium (II) (5 mg, 0.0065 mmol) were combined in CH_3CN (2 ml) and 1 M Na_2CO_3 (2 ml) and reacted in a microwave reactor for 20 min at 150°C. Water was added and the aqueous phase was extracted with DCM, dried and evaporated. Purification by reversed phase chromatography using 0-100% MeOH:water yielded 6 mg (11%) of the title compound. MS ESI (m/z): 426.7 $(M+1)^+$, calc. 425.

Example 163

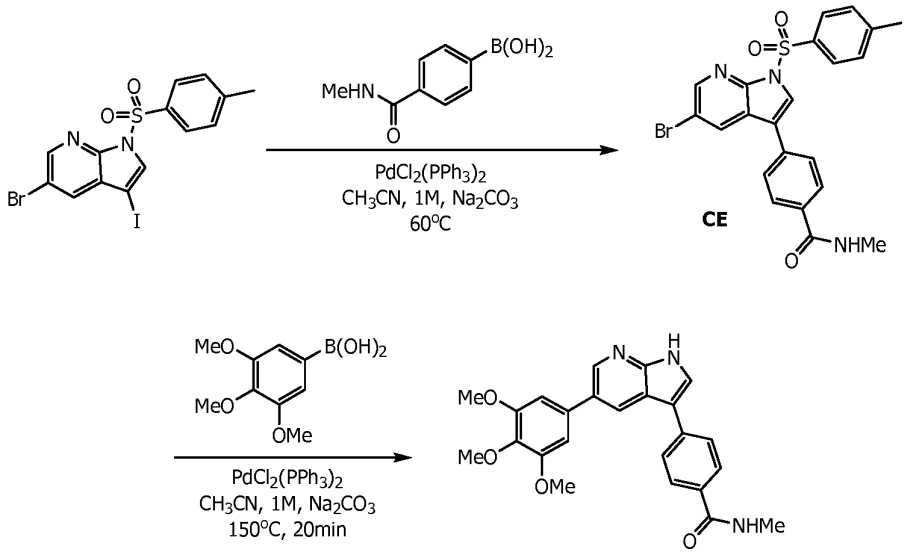
Preparation of 5-(1H-indol-5-yl)-3-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine



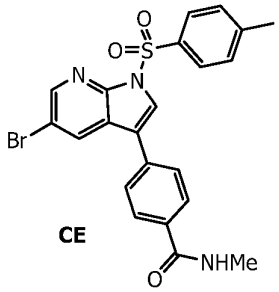
[0388] 5-(1H-Indol-5-yl)-3-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine was prepared by a method analogous to that described in *Example 162* by substituting aminocarbonylphenylboronic acid for indole-5-boronic acid. Purification by silica gel chromatography using 0-10% MeOH:DCM yielded the title compound (28 mg, 60%). MS ESI (m/z): 422.4 $(M+1)^+$, calc.421.

Example 164

Scheme 20

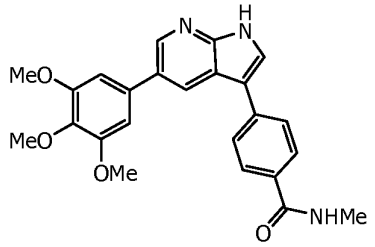


Preparation of 4-[5-bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-N-methyl-benzamide (Intermediate CE)



[0389] 5-Bromo-3-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (350 mg, 0.73 mmol), 4-(N-methylaminocarbonyl)phenylboronic acid (160 mg, 0.88 mmol) and dichlorobis(triphenylphosphine)palladium (II) (52 mg, 0.073 mmol) were combined in CH_3CN (10 ml) and 1 M Na_2CO_3 (10 ml) and stirred at 60°C for 5 hrs. Water was added and the mixture was extracted with DCM, combined organic phases were dried and evaporated to yield 428 mg (121%) of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.50 (d, J = 1.3 Hz, 1H), 8.20 (d, J = 1.2 Hz, 1H), 8.09 (d, J = 5.1 Hz, 2H), 7.94 (s, 1H), 7.87 (d, J = 5.1, 2H), 7.61 (d, J = 5.0 Hz, 2H), 7.31 (d, J = 5.0 Hz, 2H), 6.21 (bd, J = 2.5 Hz, 1H), 3.06, (d, J = 2.9 Hz, 3H), 2.39 (s, 3H).

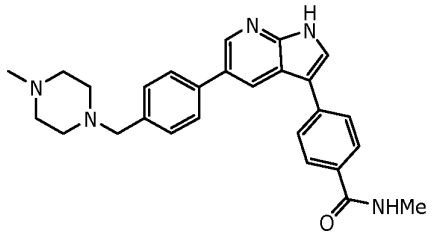
Preparation of N-methyl-4-[5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-benzamide



[0390] 4-[5-Bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-N-methyl-benzamide (Intermediate **CE**, 100 mg, 0.206 mmol), 3,4,5-trimethoxyphenylboronic acid (53 mg, 0.248 mmol) and dichlorobis(triphenylphosphine)palladium (II) (9 mg, 0.012 mmol) were combined in CH_3CN (2 ml) and 1 M Na_2CO_3 (2 ml) and reacted in a microwave reactor for 20 min at 150°C. Water was added, the aqueous phase was extracted with DCM and the organic phase was dried and evaporated. Purification by silica gel chromatography using 0-8% MeOH:DCM yielded 40 mg (47%) of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.09 (s, 1H), 8.59 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 1.2 Hz, 1H), 8.43 (q, J = 2.7 Hz, 1H), 8.04 (s, 1H), 7.94 (d, J = 4.0, 2H), 7.91 (d, J = 4.0 Hz, 2H), 7.00 (s, 2H), 3.89 (s, 6H), 3.70 (s, 3H), 2.80, (d, J = 4.5 Hz, 3H).

Example 165

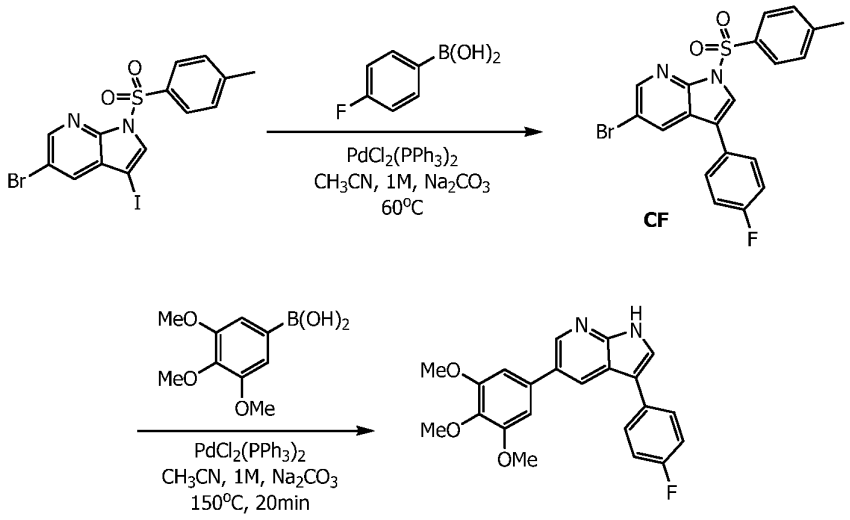
Preparation of N-methyl-4-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide



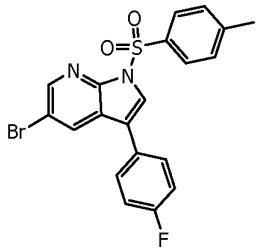
[0391] N-Methyl-4-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide was prepared by a method analogous to that described in *Example 164* by substituting 3,4,5-trimethoxyphenylboronic acid for 1-methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine. Purification by precipitation from hot DCM yielded the title compound (46 mg, 51%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.09 (s, 1H), 8.57 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 1.2 Hz, 1H), 8.43 (q, J = 2.7 Hz, 1H), 8.05 (d, J = 1.5 Hz, 1H), 7.92 (d, J = 5.2 Hz, 2H), 7.89 (d, J = 5.2 Hz, 2H), 7.73 (d, J = 4.9 Hz, 2H), 7.40 (d, J = 4.9 Hz, 2H), 3.50 (s, 2H), 2.81, (d, J = 2.7 Hz, 3H), 2.2-2.45 (bs. 8H), 2.15 (s, 3H).

Example 166

Scheme 21

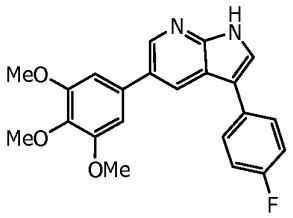


Preparation of 5-bromo-3-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate CF)



[0392] 5-Bromo-3-iodo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (70 mg, 0.147 mmol), 4-fluorophenylboronic acid (25 mg, 0.176 mmol) and dichlorobis(triphenylphosphine)palladium (II) (10 mg, 0.015 mmol) were combined in CH_3CN (2 ml) and 1 M Na_2CO_3 (2 ml) and stirred at 60°C for 3 hrs. EtOAc was added and the mixture was washed with water, dried and evaporated to yield 73 mg (112%) of the title compound. MS ESI (m/z): 445.1/447.2 $(M+1)^+$, calc. 444/446.

Preparation of 3-(4-fluoro-phenyl)-5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine

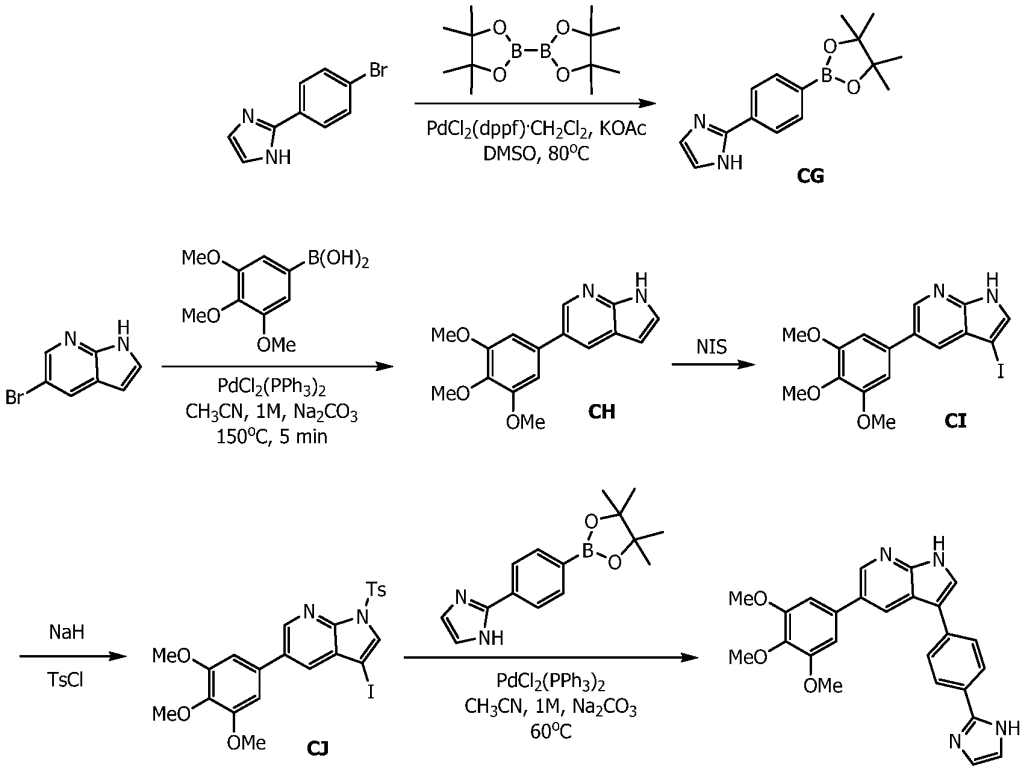


[0393] 5-Bromo-3-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (37 mg, 0.083 mmol), 3,4,5-trimethoxyphenylboronic acid (21 mg, 0.1 mmol) and

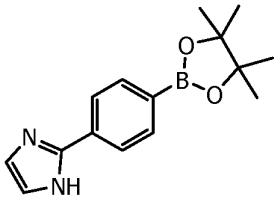
dichlorobis(triphenylphosphine)palladium (II) (3 mg, 0.004 mmol) were combined in CH_3CN (1.5 ml) and 1 M Na_2CO_3 (2 ml) and reacted in a microwave reactor for 20 min at 150°C. EtOAc was added and the mixture was washed with water, dried, evaporated and purified by silica gel chromatography using 0-2% MeOH:DCM to yield 9 mg (29%) of the title compound. MS ESI (m/z): 379.2 $(M+1)^+$, calc.378.

Example 167

Scheme 22



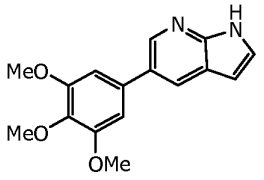
Preparation of 2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazole (Intermediate CG)



[0394] 2-(4-Bromo-phenyl)-1H-imidazole (300 mg, 1.3 mmol), bis(pinacolato)diboron (376 mg, 1.48 mmol), KOAc (400 mg, 4.03 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (50 mg, 0.067 mmol) were combined in DMSO (8 ml) and stirred t 80°C overnight. EtOAc was added, washed with water, dried, evaporated and purified by silica gel chromatography eluting with 0-5%

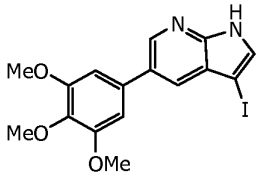
MeOH:DCM to give 116 mg (36%) of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (s, 4H), 7.18 (s, 2H), 1.36 (s, 12H).

Preparation of 5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate CH)



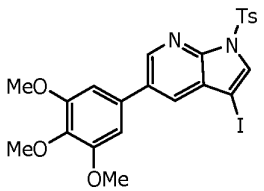
[0395] 5-Bromo-1H-pyrrolo[2,3-b]pyridine (1.54 g, 7.83 mmol), 3,4,5-trimethoxyphenylboronic acid (1.83 g, 8.61 mmol) and dichlorobis(triphenylphosphine)palladium (II) (275 mg, 0.39 mmol) were combined in CH_3CN (10 ml) and 1 M Na_2CO_3 (10 ml) and reacted in a microwave reactor for 5 min at 150°C. EtOAc was added and the mixture was washed with water, brine, dried, evaporated and purified by silica gel chromatography using 0-2% MeOH:DCM to yield 1.86 g (84%) of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.9 (bs, 1H), 8.54 (d, J = 2.1 Hz, 1H), 8.11 (d. J = 2.1 Hz, 1H), 7.41 (t, J = 2.1 Hz, 1H), 6.82 (s, 2H), 6.58 (t, J = 1.5 Hz, 1H), 3.96 (s, 6H), 3.92 (s, 3H).

Preparation of 3-iodo-5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate CI)



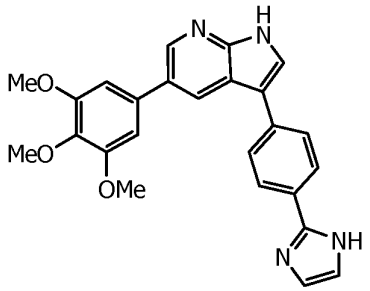
[0396] To a solution of 5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine (510 mg, 1.79 mmol) in acetone (100 ml) was added N-iodosuccinimide (444 mg, 1.97 mmol) under stirring. After 1 hr the mixture was evaporated and purified by silica gel chromatography using 0-2% MeOH:DCM to give the title compound (870 mg, 118%). MS ESI (m/z): 411.1 $(M+1)^+$, calc. 410.

Preparation of 3-iodo-1-(toluene-4-sulfonyl)-5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate CJ)



[0397] A solution of 3-iodo-5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine (870 mg, 2.12 mmol) in anh. THF (10 ml) was cooled to 0°C and NaH (60 % dispersion, 130 mg, 3.18 mmol) was added. After 20 min tosyl chloride (450 mg, 2.33 mmol) was added and the mixture was allowed to warm to room temperature. After 3 hrs the mixture was cooled to 0°C and quenched by the addition of 0.5 N HCl. The product was extracted with DCM and purified by silica gel chromatography using DCM as an eluent affording 648 mg (54%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.61 (d, J = 2.4 Hz, 1H), 8.12 (d. J = 8.4 Hz, 1H), 7.91 (s, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 6.73 (s, 2H), 3.94 (s, 6H), 3.90 (s, 3H), 2.39 (s, 3H).

Preparation of 3-[4-(1H-imidazol-2-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine

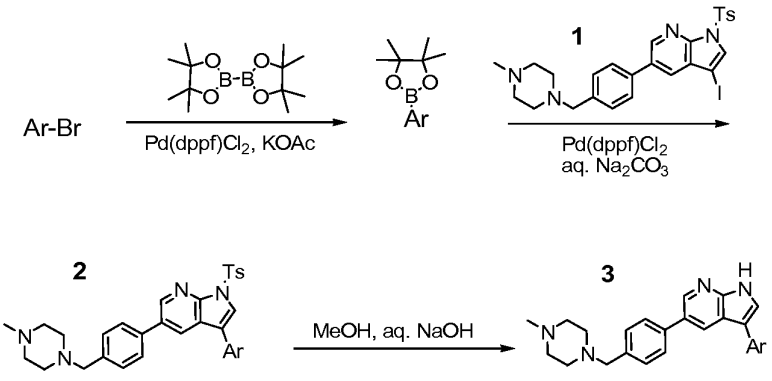


[0398] 3-Iodo-1-(toluene-4-sulfonyl)-5-(3,4,5-trimethoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate **CJ**, 30 mg, 0.053 mmol), 2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazole (Intermediate **CG**, 18 mg, 0.064 mmol) and dichlorobis(triphenylphosphine)palladium (II) (2 mg, 0.003 mmol) were combined in CH_3CN (1 ml) and 1 M Na_2CO_3 (1 ml) and stirred at 60°C for 2 d. Additional Intermediate **CG** (18 mg, 0.064 mmol) was added and stirring was continued for another day. EtOAc was added and the mixture was washed with water, dried, evaporated and purified by silica gel chromatography using 0-5% MeOH:DCM to yield 5 mg (22%) of the title compound. MS ESI (m/z): 427.2 $(M+1)^+$, calc.426.

[0399] Mass spectra for the following examples were obtained on a PE-SCIEX 150 spectrometer using API ionization mode.

Examples 171-175, 178, 180, 200-204, 206, and 221

Method Y: Synthesis via Aryl Bromides



Synthesis of 5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine

[0400] In a 100 mL rb flask, 5-bromo-7-azaindole (2 mmol), 4-(4-methyl-1-piperazynylmethyl)benzeneboronic acid pinacolester (2.2 mmol), $Pd(PPh_3)_4$ (0.01 mmol) and $NaHCO_3$ (6 mmol) were suspended in dioxane (16 mL) and water (4 mL) and heated at 110°C overnight. Upon complete consumption of starting bromide, the reaction mixture was extracted with ethyl acetate 3 times and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to afford crude product. The crude residue was purified with methylene chloride and methanol on silica gel column using ISCO to afford 5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine.

Synthesis of 3-Iodo-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine:

[0401] In a 100mL rb flask, 5-(3-Iodo-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine 4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2mmol), was dissolved in acetone (20mL) and N-iodosuccinamide (2.2mmol) was added in 3 portions with 5 min. intervals, resulting mixture was stirred at room temperature for 1 hour. Upon complete consumption of starting material, product was precipitated out as solid was filtered and washed with acetone and dried to afford pure 3-iodo-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine.

Synthesis of Method Y Intermediate 1: 3-Iodo-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine:

[0402] In a 100mL rb flask, 3-iodo-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2mmol), was suspended in THF (20mL) and NaH (3mmol) was added in 3 portions with 5 min. intervals at 0 °C, resulting mixture was stirred at 0 °C to room temperature for 1 hour. Upon complete consumption of starting material, solvents evaporated to afford crude solid was precipitated out using hexane (20mL) and cold 1N NaOH (10mL) to afford pure 3-iodo-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine.

General procedure for boronic ester synthesis:

[0403] In a microwave tube, bromo compound (1mmol), bis(pinacolato)diboron (1.1mmol), $PdCl_2$dppf (0.01mmol) and KOAc (3mmol) were suspended in acetonitrile (2mL), sealed the tube and heated at 80°C overnight. Upon complete consumption of starting bromide, extracted with ethyl acetate 3 times and combined organic layer was washed with brine and dried over Na_2SO_4 and evaporated to afford crude product. The crude residue was triturated with hexane and dried in vacuo to yield the corresponding boronic ester.

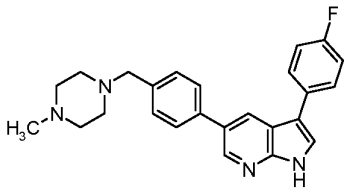
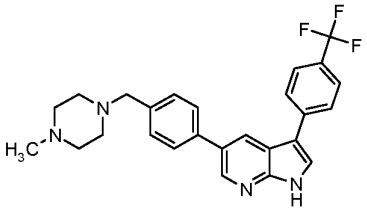
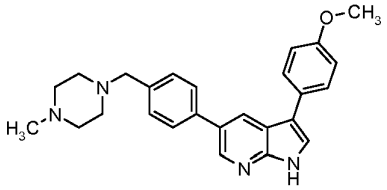
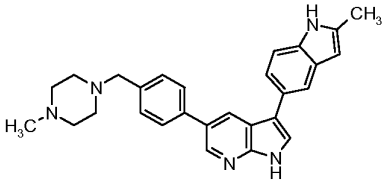
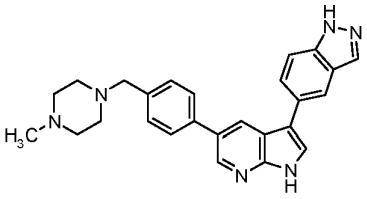
General procedure for Suzuki coupling reaction:

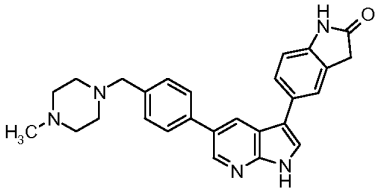
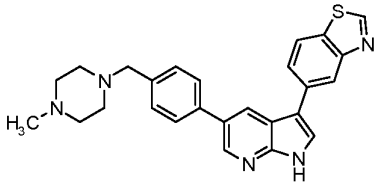
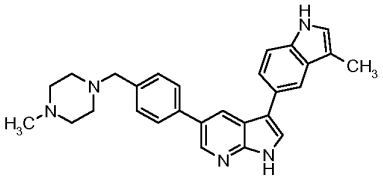
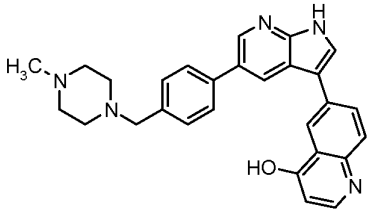
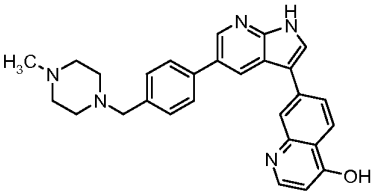
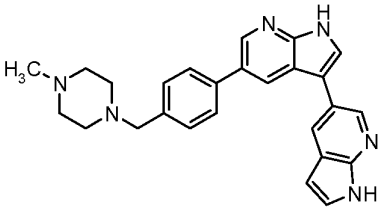
[0404] In a microwave reaction tube, intermediate 1 (2mmol), corresponding boronic ester (2.2 mmol), $PdCl_2$dppf (0.01mmol) 1M Na_2CO_3 (1mL) and acetonitrile (1mL) were heated 90 °C overnight. Upon complete consumption of starting materials, extracted with ethyl acetate 3 times and combined organic layer was washed with brine and dried over Na_2SO_4 and evaporated to afford crude product. The crude residue was purified on silicagel column on ISCO using methylene chloride and methanol.

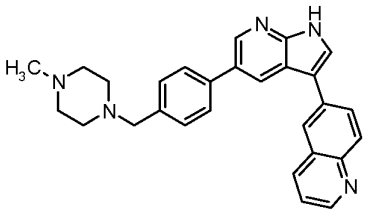
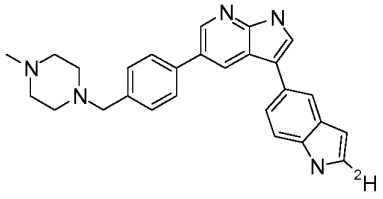
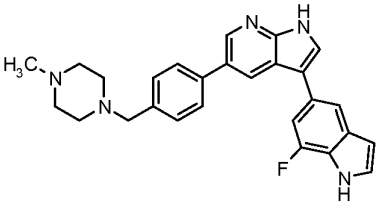
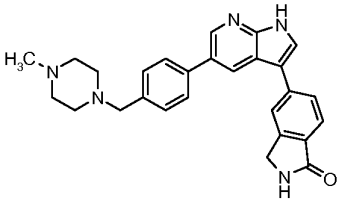
General procedure for de-tosylation reaction:

[0405] In a 50 mL rb flask, intermediate 2 (2mmol) was treated with 1N NaOH (2mL) in methanol (2mL) were heated 60°C for 2 hours. Upon complete consumption of starting material, extracted with ethyl acetate 3 times and combined organic layer was washed with brine and dried over Na_2SO_4 and evaporated to afford crude product. The crude residue was purified on silicagel column on ISCO using methylene chloride and methanol.

[0406] Using the corresponding aryl bromides the following compounds were prepared using method Y.

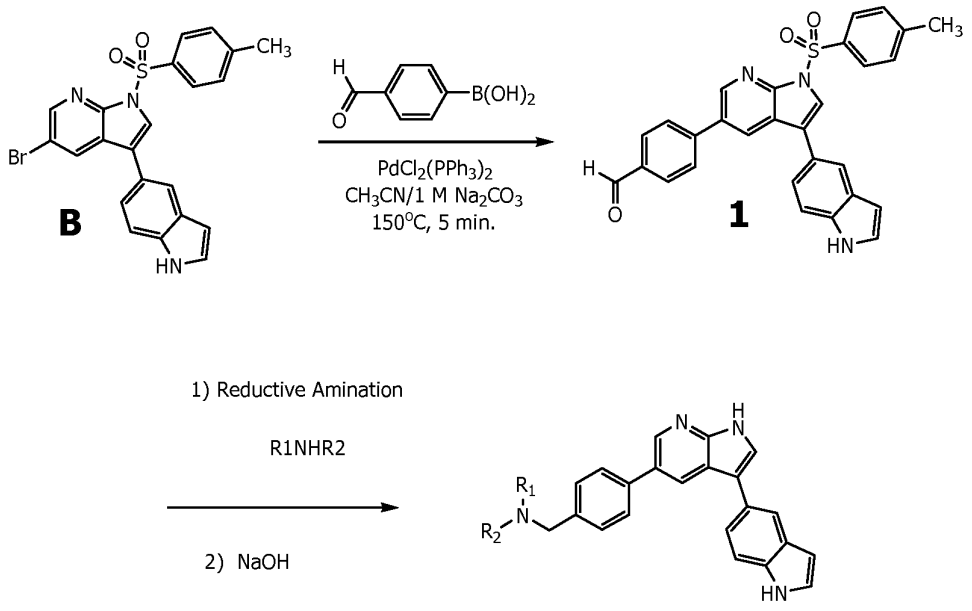
Example	Structure	M+H
170		401
171		451
172		413
173		436
174		423

Example	Structure	M+H
175		438
178		440
180		436
200		450
201		450
202		423

Example	Structure	M+H
203		434
206		423
204		440
221		437.55

Examples 169, 177, and 178

Method X: Reductive Amination

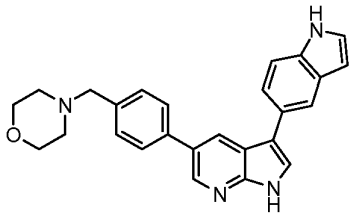


Synthesis of Method X Intermediate 1: 4-(3-(1H-indol-5-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-5-yl)benzaldehyde

[0407] Intermediate B (4.04 g) and 4-formylphenylboronic acid (1.56 g) were suspended in 150 mL of acetonitrile and treated with 150 mL of 1 M sodium carbonate solution. To this was added dichloro-bis-(triphenylphosphine)-palladium(II) (608 mg) and the mixture was heated at reflux for 2.5 hours. The reaction mixture was filtered and the residue washed with EtOAc, the filtrates were combined and washed with water, and brine, dried over MgSO4, and concentrated. MPLC silica gel chromatography eluting with 0 -30% EtOAc in hexane, produced 3.77 g of the title compound (M+H 492).

Example 169

Preparation of 4-(4-(3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)benzyl)morpholine

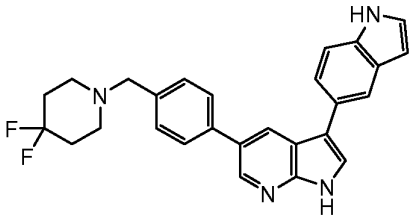


[0408] Intermediate **1** (60 mg) was suspended in anhydrous methanol (3 mL), dichloromethane (0.5 mL) and THF (1.5 mL) and treated with morpholine (45 uL) and stirred for 10 minutes, to this was added sodium triacetoxy borohydride 39 mg, the reaction stirred over night and was diluted with water and extracted with dichloromethane. The organic layers were

washed with brine and dried over MgSO4 and purified by MPLC silica gel chromatography (50-100% EtOAc in hexane) to yield an analytical sample (28 mg, M+H 563). The tosyl group was removed using the general procedure for hydrolysis above, and the resulting material was purified by crystallization from EtOH/water to give 10 mg (M+H, 609) of an analytical sample of the title compound.

Example 177

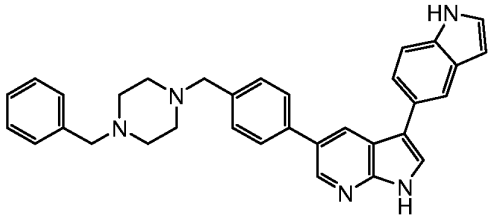
Preparation of 5-(4-((4,4-difluoropiperidin-1-yl)methyl)phenyl)-3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridine



[0409] Intermediate **1** (50 mg) was dissolved in anhydrous dichloromethane (3 mL) and treated with 33 mg of 4,4-difluro-piperidine, to this was added activated 4 A molecular sieves, and the mixture stirred 1.5 hrs, to this was added 33 mg of sodium triacetoxy borohydride, and the reaction stirred overnight. The reaction was diluted with dichloromethane and washed with water, brine and dried over $MgSO_4$. MPLC purification on silica gel (30- 70% EtOAc in hexane) provided 45 mg of crude product. Hydrolysis according to the general method above provided the de-tosylated compound which was purified by MPLC silica gel chromatography (2% MeOH in DCM) to provide the title compound (M+H 443)

Example 178

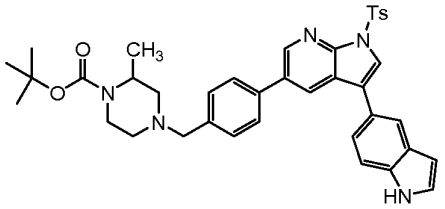
Preparation of (4-((4-benzylpiperazin-1-yl)methyl)phenyl)-3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridine



[0410] Intermediate **1** (100 mg) was dissolved in anhydrous dichloromethane (3 mL) and treated with 54 mg of 4-benzylpiperazine, to this was added activated 4 angstrom molecular

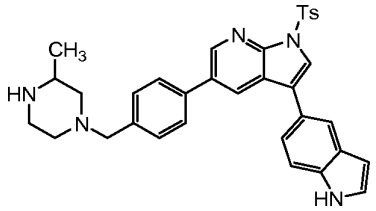
sieves, and the mixture stirred 2 hrs. To this mixture, was added 65 mg of sodium triacetoxy borohydride, and the reaction stirred overnight. The reaction was diluted with dichloromethane and washed with water, brine and dried over MgSO4. MPLC purification on silica gel (0-2% MeOH in dichoromethane) provided 69 mg of crude product. Hydrolysis according to the general method above provided the de-tosylated compound which was purified by MPLC silica gel chromatography (2% MeOH in DCM) to provide 45 mg of the title compound (M+H 498)

Preparation of *tert*-butyl 4-(4-(3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzyl)-2-methylpiperazine-1-carboxylate



[0411] Intermediate **1** (50 mg) was dissolved in anhydrous dichloromethane (3 mL) and treated with 41 mg of *tert*-butyl 2-methylpiperazine-1-carboxylate. To the resulting solution was added activated 4 Å molecular sieves, and the mixture was stirred 2 hrs at room temperature. 33 mg of sodium triacetoxy borohydride was added, and the reaction was stirred overnight, after which it was diluted with dichloromethane, washed with water and brine, and dried over $MgSO_4$ to yield the title compound.

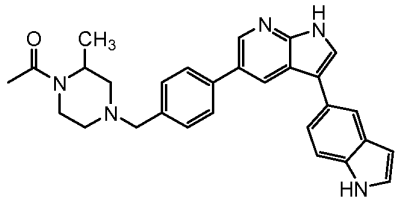
Preparation of 3-(1H-indol-5-yl)-5-(4-((3-methylpiperazin-1-yl)methyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine



[0412] The Boc protected compound above was dissolved in dichloromethane, and treated with 2 mL of TFA, stirred 30 minutes, the solvent was removed *in vacuo* and the residue was taken up in dichloromethane and washed with sodium hydroxide solution, water and brine to yield 80 mg of crude material.

Example 197

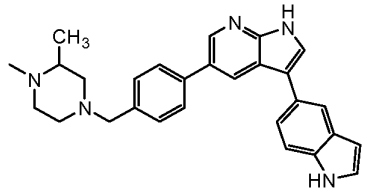
Preparation of 1-(4-(4-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzyl)-2-methylpiperazin-1-yl)ethanone



[0413] 3-(1*H*-indol-5-yl)-5-(4-((3-methylpiperazin-1-yl)methyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (50 mg) was suspended in 1 mL dichloromethane and 1 mL of methanol and treated with triethylamine (100 mL) and acetic anhydride (20 μL) and stirred for one hour. The mixture was concentrated in vacuo, taken up in EtOAc and washed with water and brine and dried over MgSO4. The residue was suspended in methanol and treated with 5 N NaOH and heated at 50°C for one hour. The mixture was diluted with dichloromethane and washed with water and brine, dried over $MgSO_4$ and purified by MPLC silica gel chromatography (0 -20% MeOH in DCM) to yield an analytical sample (464 M+H).

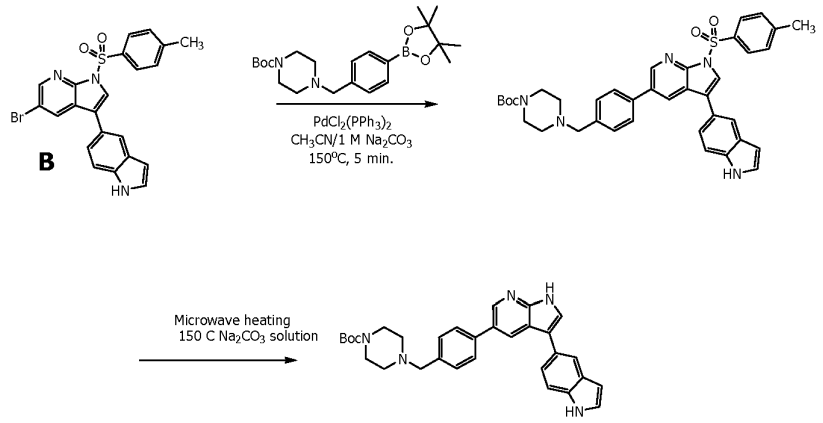
Example 198

5-(4-((3,4-dimethylpiperazin-1-yl)methyl)phenyl)-3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridine



[0414] 3-(1H-indol-5-yl)-5-(4-((3-methylpiperazin-1-yl)methyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (40 mg) was suspended in 3 mL of methanol and THF (1 mL) and treated with paraformaldehyde (~ 50 mg) and stirred for one hour. To this was added 50 mg of sodium triacetoxyborohydride. The reaction stirred 1 hr at room temperature. The mixture was concentrated *in vacuo*, taken up in EtOAc and washed with water and brine and dried over MgSO4. The residue was suspened in methanol and treated with 5 N NaOH and heated at 50 C for one hour. The mixture was diluted with dichloromethane and washed with water and brine, dried over MgSO4 and purified by MPLC silica gel chromatography (0 -20% MeOH in DCM) to yield an analytical sample 10 mg (436 M+H).

Analogs via Suzuki Method as in Example 144

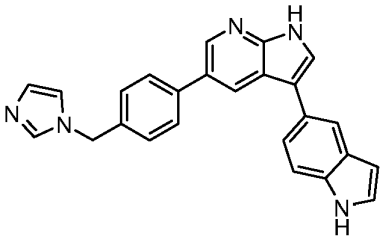


Preparation of *tert*-butyl 4-(4-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzyl)piperazine-1-carboxylate

[0415] Intermediate **B** (131 mg) and *tert*-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine-1-carboxylate (136 mg) were suspended in 2 mL of acetonitrile and treated with 2 mL of 1 M sodium carbonate solution and dichloro-bis-(triphenylphosphine)-palladium(II) (10 mg). The resulting mixture was heated in a microwave reactor cell for 20 minutes at 150°C, resulting in de-tosylated material which was purified by MPLC chromatography (0 -3% methanol) to provide an analytical sample of the title compound (50 mg, 508 M+H).

Example 199

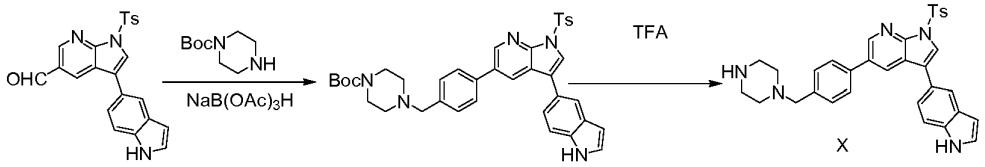
Preparation of 5-(4-((1*H*-imidazol-1-yl)methyl)phenyl)-3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine

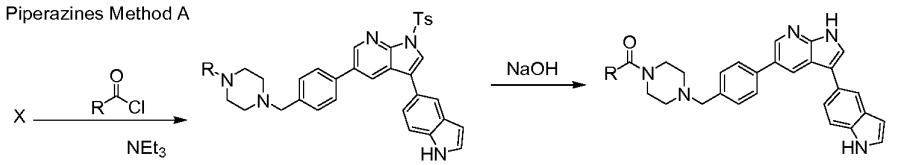


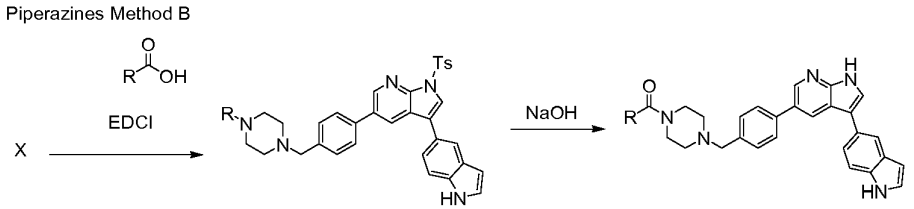
[0416] Intermediate **B** (50 mg) and 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1*H*-imidazole (37 mg) were suspended in 2 mL acetonitrile and 2 mL 1 M sodium carbonate solution, treated with dichloro-bis-(triphenylphosphine)-palladium(II) (8 mg) and microwaved 15 minutes at 150°C to produce the detosylated product. Water was added to the cooled reaction mixture, which was then extracted with EtOAc. The combined organic layers

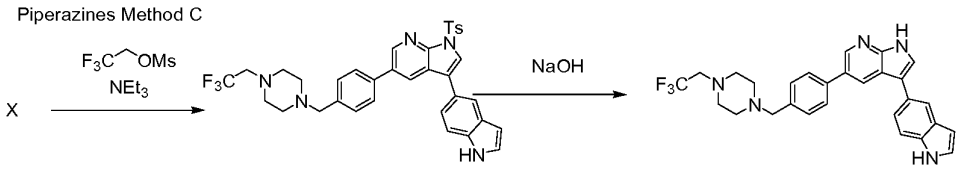
were washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by MPLC silica gel chromatrography (0 -20 % MeOH in dichloromethane) and recrystallized from EtOH/water, to yield 22 mg of an analytical sample (390 M+H).

Piperazines Methods A – C

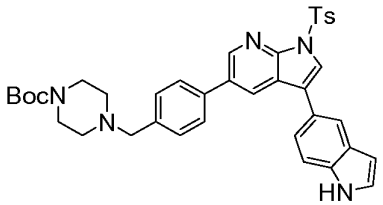








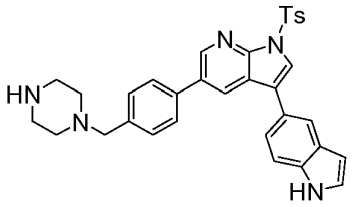
Preparation of *tert*-butyl 4-(4-(3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzyl)piperazine-1-carboxylate



[0417] 4-(3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzaldehyde (2.1 g) was suspended in anhydrous dichloromethane (15 mL), treated with *tert*-butyl piperazine-1-carboxylate (1.6 g), and stirred for one hour. To the resulting mixture was added sodium triacetoxy borohydride 1.36 g in three portions. The reaction was stirred for 3 hours, diluted with water and extracted with dichloromethane. The organic layers were washed with brine,

dried over $MgSO_4$, and purified by MPLC silica gel chromatography (30-60% EtOAc in hexane) to yield 2.62g of the title compound (M+H 662).

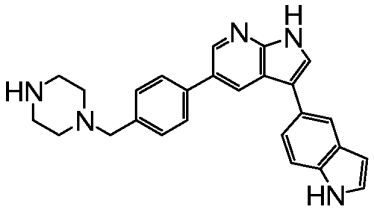
Preparation of 3-(1H-indol-5-yl)-5-(4-(piperazin-1-ylmethyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine



[0418] tert-butyl 4-(4-(3-(1H-indol-5-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-5-yl)benzyl)piperazine-1-carboxylate (500 mg) was suspended in 6 mL of dichloromethane and treated with TFA (5 mL) and reacted for 30 minutes. The solvent was removed in vacuo and the residue washed with 1 N sodium hydroxide solution, water and brine and dried over $MgSO_4$ to yield 418 mg of crude product that was used without further purification (562 M+H).

Example 168

3-(1*H*-indol-5-yl)-5-(4-(piperazin-1-ylmethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine



[0419] *tert*-butyl 4-(4-(3-(1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzyl)piperazine-1-carboxylate (63 mg) was suspended in dichloromethane (2 mL) and treated with TFA (2 mL). The resulting mixture was stirred for 90 minutes at room temperature, after which the solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with 10% sodium hydroxide solution, water, and brine. The organic layer was dried over $MgSO_4$, and the solvent was removed *in vacuo*. MPLC silica gel chromatography (0 -20% MeOH in dichloromethane) provided an analytical sample (10 mg, 408 M+H) of the title compound.

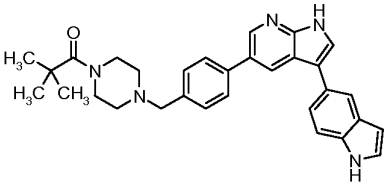
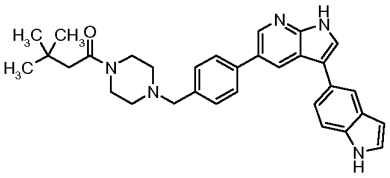
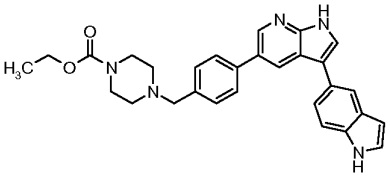
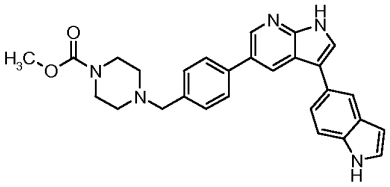
Examples 181-190

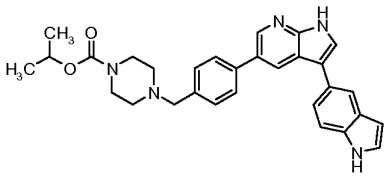
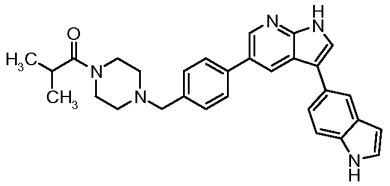
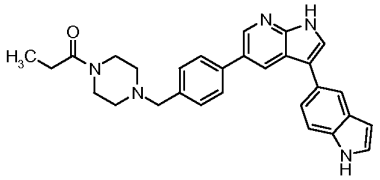
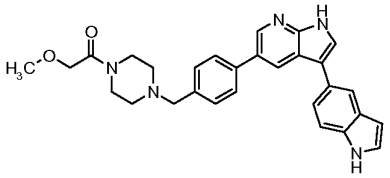
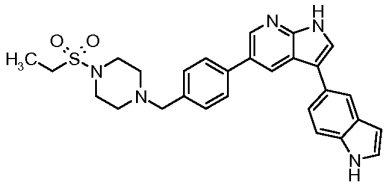
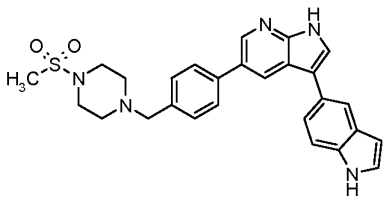
General Method A: Electrophiles Parallel Synthesis

[0420] 3-(1H-indol-5-yl)-5-(4-(piperazin-1-ylmethyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (40 mg) was dissolved in a mixture of acetonitrile (0.5 mL), methanol (0.5 mL), THF

(1 mL) and treated with 100 microliters of triethylamine. To this mixture was added a solution of 200 μL of a 10% solution of the designated electrophile in acetonitrile. After one hour the reaction was treated with an additional 200 μL of the electrophile solution and the reactions were allowed to stir for approximately 15 hours. The products were detosylated directly by the addition of 0.5 mL sodium hydroxide solution, followed by stirring over night and heated to 50 C for one hour. The reactions were diluted with water, extracted with dichloromethane and purified by MPLC, on silica gel, eluting with methanol in dichloromethane.

[0421] The following compounds were synthesized by this route:

Example	Structure	M+H	Electrophile
181		492	2,2-dimethyl-propanic acid
182		506	3,3,-dimethyl-butanoic acid
183		480	ethyl chloroformate
184		466	methyl chloroformate

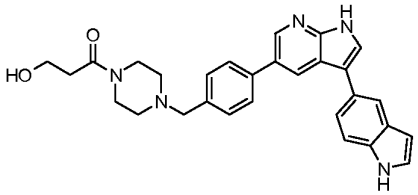
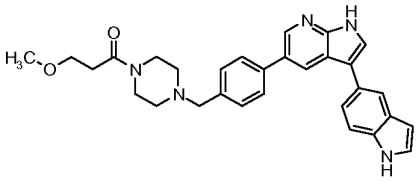
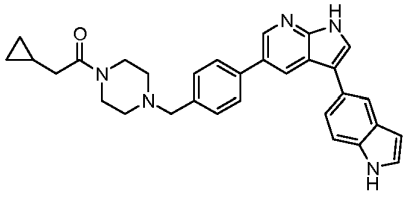
Example	Structure	M+H	Electrophile
185		494	isobutyl chloroformate
186		478	2-methyl propionyl chloride
187		464	Propionyl chloride
188		480	2-methoxy acetyl chloride
189		500	Ethane sulfonyl chloride
190		486	Methane sulfonyl chloride

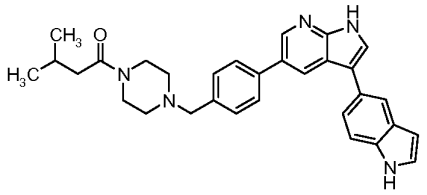
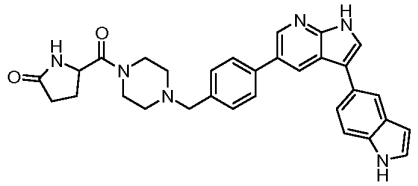
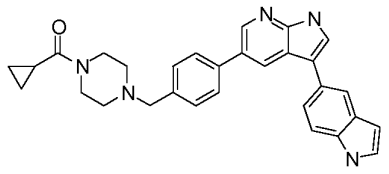
Examples 191-195 and 207

General Method B: Carbodiimide Couplings Parallel Synthesis

[0422] 3-(1H-indol-5-yl)-5-(4-(piperazin-1-ylmethyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (50 mg) was dissolved in a mixture of acetonitrile (1 mL), methanol (1 mL), THF (1 mL) and the corresponding carboxylic acids (20 mg) then treated with N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (22 mg). The reactions were allowed to stir for approximately 15 hours, diluted with dichloromethane and washed with 1 N sodium hydroxide, water and brine and evaporated. The products were suspended in MeOH and (2 mL) detosylated directly by the addition of 0.5 mL sodium hydroxide solution, followed by stirring over night and heated to 50 C for one hour. The reactions were diluted with water, extracted with dichloromethane and purified by MPLC, on silica gel, eluting with methanol in dichloromethane.

[0423] The following compounds were synthesized by this route:

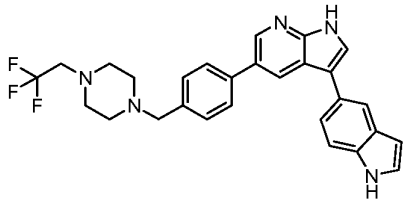
Example	Structure	M+H	Acids
191		480	3-hydroxypropanoic acid
192		494	3-methoxypropanic acid
193		490	2-cyclopropylacetic acid

Example	Structure	M+H	Acids
194		492	3-methyl-butanoic acid
195		519	5-oxopyrrolidine-2-carboxylic acid
207		476	Cyclopropane carboxylic acid

Method C: Reaction with highly reactive mesylates

Example 196

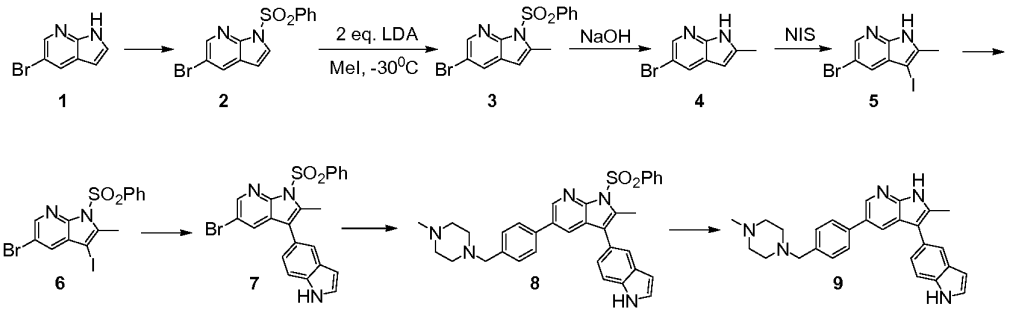
3-(1*H*-indol-5-yl)-5-(4-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine



[0424] 3-(1*H*-indol-5-yl)-5-(4-(piperazin-1-ylmethyl)phenyl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (50 mg) was dissolved in THF (1 mL) and treated with triethylamine (13 uL), and 2,2,2-trifluoroethyl methanesulfonate (13 uL); the reaction was allowed to stir for approximately 15 hours, diluted water and extracted with EtOAC and washed with 1 N sodium hydroxide, water and brine and evaporated. The product was suspended in MeOH and (2 mL) detosylated directly by the addition of 0.5 mL sodium hydroxide solution, heated to 50 C for one hour. The reaction was diluted with water, extracted with dichloromethane and purified by MPLC, on silica gel, eluting with methanol in dichloromethane to yield 6 mg of an analytical sample (490 M+H).

Example 205

Method A: Synthesis of 2-Methylazaindole Derivatives



Preparation of Method A Intermediate 2: 1-Benzenesulfonyl-5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine

[0425] 5-Bromoazaindole (**1**, 2.00 g, 10.1 mmol), tetrabutylammonium bromide (0.03 eq, 0.25 mmol, 82 mg) and powdered NaOH (3 eq, 30.45 mmol, 1.22 g) are combined in DCM (100 ml) and cooled to 0°C. Phenylsulfonyl chloride (1.25 eq, 12.69 mmol, 1.62 mL) is added dropwise. After the addition is completed the mixture is stirred for 2h at 0°C. The mixture is filtered, absorbed on Celite and purified by silica gel chromatography with a 40 to 60% gradient of EtOAc in hexane. 2.58 g (7.65 mmol, 75% yield) of **2** is obtained. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.45 (d, *J* = 1.8 Hz, 1H), 8.17 (m, 2 H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.74 (d, *J* = 3.9 Hz, 1H), 7.60 (m, 1H), 7.50 (m, 2H), 6.55 (d, *J* = 3.9 Hz, 1H). MS (m/z): 338 (M+H).

Preparation of Method A Intermediate 3: 1-Benzenesulfonyl-5-bromo-2-methyl-1H-pyrrolo[2,3-b]pyridine

[0426] To a solution of diisopropylamine (2.8 eq, 1.66 mmol, 240 µL) in THF (2 ml) at -10°C is added *n*-butyllithium (1.6 M in hexane, 2.6 eq, 1.54 mmol, 965 l) dropwise. The mixture is allowed to stir for 30 min and then cooled to -35°C. A solution of compound **2** (1 eq., 200 mg, 0.593 mmol) in THF is added dropwise and the mixture is stirred for 30 min at -35°C. Iodomethane (3 eq, 1.78 mmol, 111 µL) is added in a dropwise fashion and the mixture is stirred for 2 h while warming up to room temperature. The reaction is quenched by addition of a saturated NH_4Cl solution, extracted with EtOAc and purified by silica gel chromatography (stepwise gradient of 0 to 15% EtOAc in hexane). 126 mg (0.359 mmol, 60%) of compound **3** are obtained. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.37 (d, *J* = 2.4 Hz, 1H), 8.12 (m, 2 H), 7.81 (d, *J* =

2.4 Hz, 1H), 7.58 (m, 1H), 7.50 (m, 2H), 6.24 (d, J = 1.2 Hz, 1H), 2.73 (d, J = 1.2 Hz, 3H). MS (m/z): 352 (M+H).

Preparation of Method A Intermediate 4: 5-Bromo-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine

[0427] Starting material **3** (88 mg, 0.251 mmol) is dissolved in MeOH (4 ml), 2 N NaOH (1 ml) is added and the mixture is refluxed for 2 h. EtOAc is added and the organic phase is washed with 1 N NaOH and water. After purification by silica gel chromatography (slow gradient from 0 to 2% MeOH in DCM), 40 mg (0.19 mmol, 76%) of **4** is obtained. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.26 (bs, 1H), 8.22 (d, J = 2.1 Hz, 1H), 8.92 (d, J = 2.1 Hz, 1H), 6.13 (s, 1H), 2.52 (s, 3H). MS (m/z): 210 (M+H).

Preparation of Method A Intermediate 5: 5-Bromo-3-iodo-2-methyl-1H-pyrrolo[2,3-b]pyridine

[0428] A mixture of **4** (85 mg, 0.378 mmol) and N-iodosuccinimide (1.1 eq, 0.42 mmol, 95 mg) in acetone (1.5 ml) is stirred for 1 h at room temperature. The precipitate is filtered off, washed with cold acetone and dried to yield 90 mg (0.267 mmol, 71 %) of the desired product.

Preparation of Method A Intermediate 6: 1-Benzenesulfonyl-5-bromo-3-iodo-2-methyl-1H-pyrrolo[2,3-b]pyridine

[0429] Compound **5** (90 mg, 0.267 mmol), tetrabutylammonium bromide (0.025 eq, 0.0067 mmol, 3 mg) and powdered NaOH (3 eq, 0.8 mmol, 32 mg) are combined in DCM (3 ml) and cooled to 0°C. Phenylsulfonyl chloride (1.25 eq, 0.334 mmol, 43 l) is added dropwise. After the addition is completed the mixture is stirred for 15 min at 0°C and then allowed to warm up to room temperature over 2h. The mixture is filtered, absorbed on Celite and purified by silica gel chromatography eluting with DCM. 112 mg (0.235 mmol, 88% yield) of **6** is obtained.

Preparation of Method A Intermediate 7: 1-Benzenesulfonyl-5-bromo-3-(1H-indol-5-yl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine

[0430] A mixture of **6** (112 mg, 0.235 mmol), 5-indoleboronic acid (1.1 eq, 0.26 mmol, 42 mg) and dichlorobis(triphenylphosphine)palladium(II) (0.05 eq, 0.0118 mmol, 8.5 mg) in MeCN (3 ml) and 1 M Na_2CO_3 (3 ml) is stirred at 45°C for 1h. Water is added, and the mixture is extracted with EtOAc and purified by silica gel chromatography (0 to 40% stepwise gradient of EtOAc in hexane). 76 mg (0.163 mmol, 69%) of the desired product **7** are obtained.

Preparation of Method A Intermediate 8: 1-Benzenesulfonyl-3-(1H-indol-5-yl)-2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine

[0431] A mixture of **7** (76 mg, 0.163 mmol), 1-methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine (1.2 eq, 0.196 mmol, 62 mg) and dichlorobis(triphenylphosphine)palladium(II) (0.05 eq, 0.008 mmol, 6 mg) in MeCN (2.5 ml) and 1 M Na_2CO_3 (2 ml) is reacted at 150°C for 5 min by microwave reactor (Biotage initiator). Water is added, and the mixture is extracted with EtOAc and purified by silica gel chromatography (0 to 20% gradient of MeOH in DCM). A mixture of the desired product **8** with some deprotected material **9** is obtained.

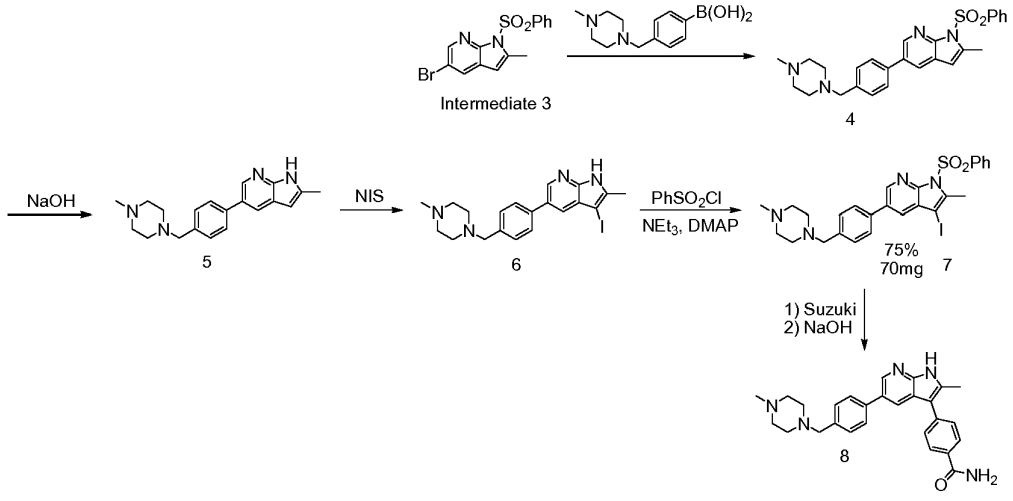
Preparation of Example 205: 3-(1H-Indol-5-yl)-2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine

[0432] The mixture obtained in the last step is dissolved in MeOH (4 ml), 2 N NaOH (1 ml) is added and refluxed for 2 h. EtOAc is added and the organic phase is washed with 1 N NaOH and water. After purification by silica gel chromatography (gradient from 0 to 20% MeOH in DCM) 5 mg of **9** are obtained. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.89 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 8.15 (s, 1H), 7.76 (s, 1H), 7.53 (m, 3H), 7.37 (m, 3H), 7.27 m, 1H), 6.62 (s, 1H), 3.56 (s, 2H), 2.63 (s, 3H), 2.53 (bs, 8H) 2.32 (s, 3H). MS (m/z): 436 (M+H).

Example 220

Method B: Synthesis of 2-Methyl Azaindoles

4-(2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzamide



Preparation of Method B Intermediate 4: 2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine

[0433] 1-Benzenesulfonyl-5-bromo-2-methyl-1H-pyrrolo[2,3-b]pyridine (378 mg, 1.076 mmole) and 4-((4-methylpiperazin-1-yl)methyl)phenylboronic acid (303 mg, 1.29 mmole) are dissolved in acetonitrile (10 mL) and treated with 10 mL 1 M sodium carbonate solution. To this is added 40 mg of $PdCl_2(PPh_3)_2$ catalyst, and the mixture is irradiated for 5 minutes at 150 degrees in a Biotage microwave reactor. After cooling, the reaction mixture is diluted with water and extracted with ethyl acetate, dried, and concentrated. MPLC silica gel chromotagraphy 5 – 20% MeOH in dichloromethane gradient elution, provided 367 mg of the title compound as a solid.

Preparation of Method B Intermediate 5: 2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrrolo[2,3-b]pyridine

[0434] Intermediate 4 (367 mg) in 4 mL MeOH, was treated with 1.2 mL of 2 N NaOH and stirred 15 hours at room temperature, then refluxed 2 hours, and cooled. The volatiles were removed on a rotovap, and partitioned between EtOAc and 1 N NaOH solution. The EtOAc layers were washed with water and saturated sodium chloride solution and dried over MgSO4. The solvent was removed in vacuo to produce 204 mg of crude material (M+H 321).

Preparation of Method B Intermediate 6: 3-iodo-2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrrolo[2,3-b]pyridine

[0435] Intermediate 5 (204 mg, 0.637 mmole) was dissolved in 10 mL acetone and treated with 160 mg of iodosuccinimide. The reaction stirred 1 hour at room temperature and the product was collected by filtration and purified by MPLC silica gel chromatography by a 0 -10% gradient of MeOH in dichloromethane to yield 215 mg of the title compound.

Preparation of Method B Intermediate 7: 3-iodo-2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine

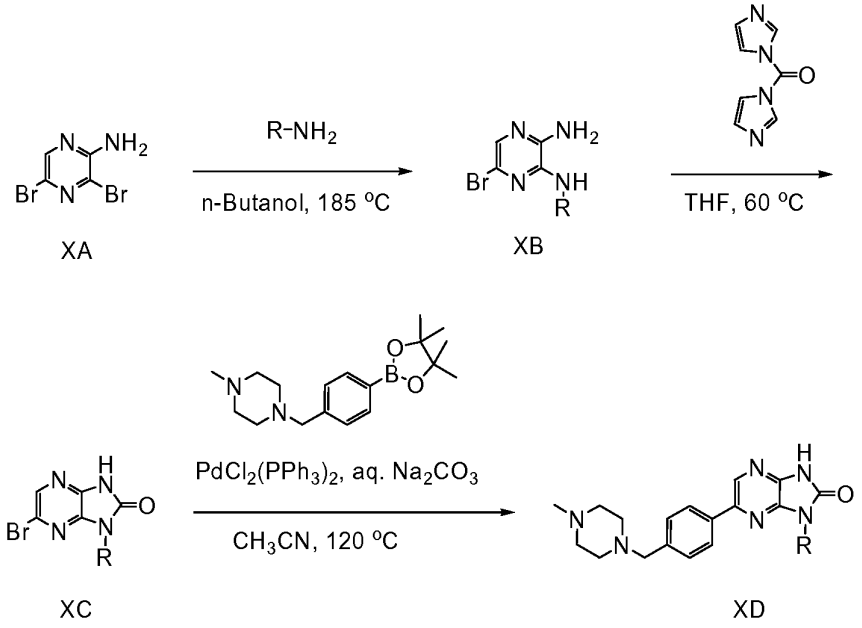
[0436] Intermediate 6 (70 mg) in dichloromethane (10 mL) was treated with triethylamine (70 microliters) DMAP (5 mg) and benzenesulfonyl chloride (30 microliters) and stirred 24 hours, an additional 30 microliters of benzenesulfonyl chloride was added and stirred for an additional 24 hours. The reaction mixture was diluted with dichloromethane and washed with 1 N NaOH, water, and sodium chloride solution and dried over MgSO4. Removal of solvent *in vacuo* produced 70 mg of the crude title compound.

Preparation of 4-(2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzamide (8)

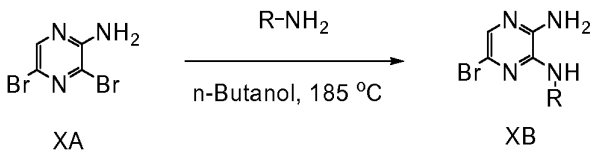
[0437] Intermediate 7 (70 mg) and the 4-benzamide boronic acid (24 mg) was dissolved in 5 mL of acetonitrile and mixed with 5 mL of 1 M sodium carbonate solution and treated with $Pd(Cl_2)(PPh_3)_2$ catalyst (9 mg), the reaction stirred 2 hours at 60 C. After cooling the mixture was diluted with EtOAc and washed with water and sodium chloride solution and dried over MgSO4. The crude material was suspended in MeOH (3.5 mL), treated with 1 mL of 2 N NaOH solution and refluxed 2 hr. The mixture was extracted with EtOAc and extracts were washed with 1 N NaOH, water and sodium chloride solution, and dried over MgSO4. Reverse phase chromatography (C18) eluting with a 0 -100% methanol gradient in water provided an analytical sample, 15 mg of the title compound as a solid. (440, M+H).

Examples 224-233 and 235-238

Scheme 23

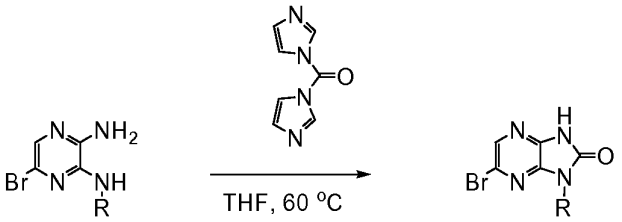


Preparation of 4-(3-Amino-6-bromo-pyrazin-2-ylamino)-aryl/hetero-aryl/alkyl intermediates XB



[0438] To a stirred suspension of 3,5-dibromopyrazin-2-amine (2.0 g, 7.93 mmol) and the in n-butanol (8 mL) was added corresponding alkyl, aryl, or heteroaryl amine (1.37g, 10.31 mmol). The resulting mixture was stirred for 2 hrs at 185°C, after which it was partitioned between EtOAc and H_2O. The organic layer was separated, after which it was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to yield a residue that was purified by automated medium pressure silica gel chromatography eluting with 1:1 EtOAc:hexanes to yield the XB intermediates as amorphous solids.

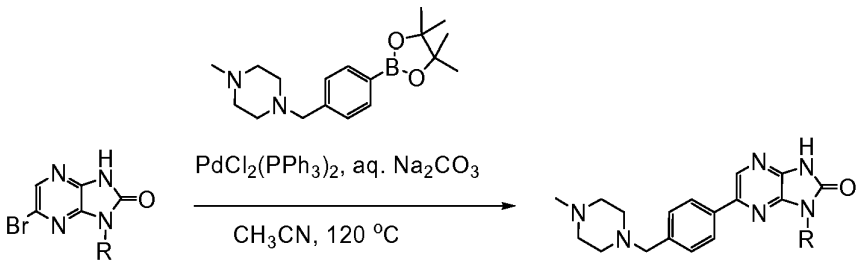
Preparation of 6-Bromo-1-(4-aryl/hetero-aryl/alkyl)-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one intermediates XC



XB XC

[0439] Intermediates XB (2.5 g, 8.19 mmol) were dissolved in THF (40 mL) and treated with carbonyldiimidazole (7.96 g, 49.18 mmol). The resulting mixture was heated at 65°C for 24-48 hr, after which it was concentrated *in vacuo* and partitioned between EtOAc and H_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a residue that was purified via automated silica gel chromatography eluting with hexane/EtOAc to yield the intermediates XC as amorphous solids.

Preparation of 1-aryl/hetero-aryl/alkyl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one compounds



XC XD

[0440] Individual solutions of intermediates XC (0.18 mmol) in CH_3CN (2 mL) in a Personal Chemistry microwave reaction vial was added the 1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine (0.21 mmol), bis(triphenylphosphine)-palladium(II) dichloride (2.1 mg, 0.003 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 30 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue was purified by preparatory HPLC to yield the title compounds in Table 4 (>5 mg) as amorphous solids.

Table 4.

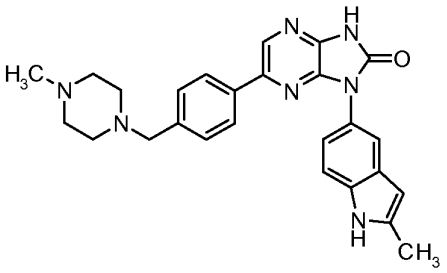
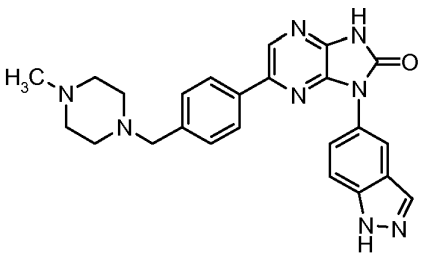
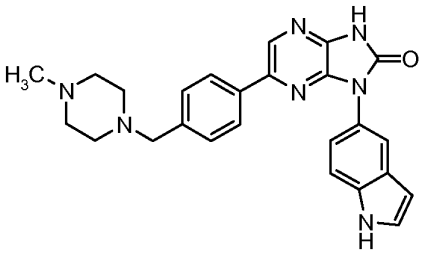
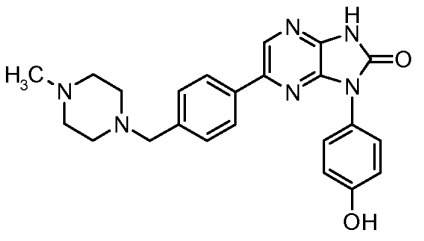
Example	Boronic Acid	Amine	Purified Compound Isolated
224	1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	2-Methyl-1H-indol-5-ylamine	1-(2-Methyl-1H-indol-5-yl)-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
225	1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	1H-Indazol-5-ylamine	1-(1H-Indazol-5-yl)-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
226	1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	1H-Indol-5-ylamine	1-(1H-Indol-5-yl)-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
227	1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	4-Amino-phenol	1-(4-Hydroxy-phenyl)-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
228	1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	Benzothiazol-5-ylamine	1-Benzothiazol-5-yl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one

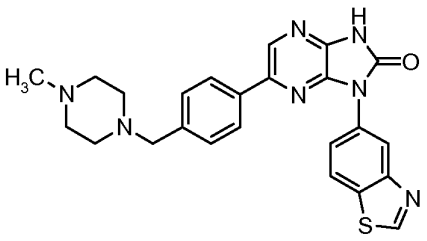
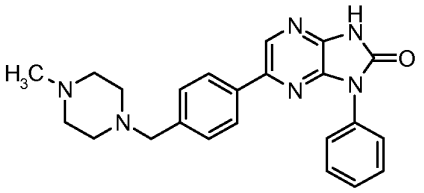
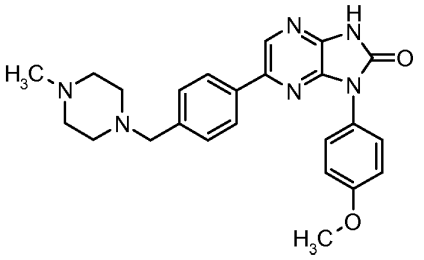
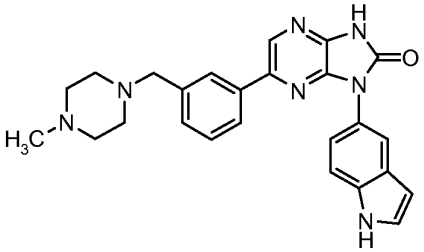
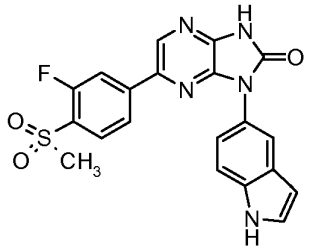
229	1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	Phenylamine	6-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1-phenyl-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
230	1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	4-Methoxy-phenylamine	1-(4-Methoxy-phenyl)-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
231	1-Methyl-4-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	1H-Indol-5-ylamine	1-(1H-Indol-5-yl)-6-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
232	3-Fluoro-4-(methylsulfonyl)phenyl boronic acid	1H-Indol-5-ylamine	6-(3-Fluoro-4-methanesulfonyl-phenyl)-1-(1H-indol-5-yl)-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
233	3-Fluoro-4-methoxyphenylboronic acid	1H-Indol-5-ylamine	6-(3-Fluoro-4-methoxy-phenyl)-1-(1H-indol-5-yl)-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
235	1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	Indan-2-ylamine	1-Indan-2-yl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
236	1-Methyl-4-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	Indan-2-ylamine	1-Indan-2-yl-6-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
237	1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine	C-Cyclopropyl-methylamine	1-Cyclopropylmethyl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one
238	1-Methyl-4-[3-(4,4,5,5-tetramethyl-	C-Cyclopropyl-methylamine	1-Cyclopropylmethyl-6-[3-(4-methyl-piperazin-1-ylmethyl)-

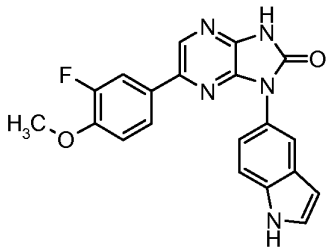
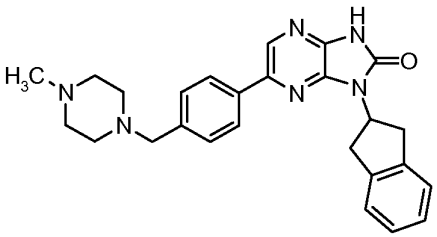
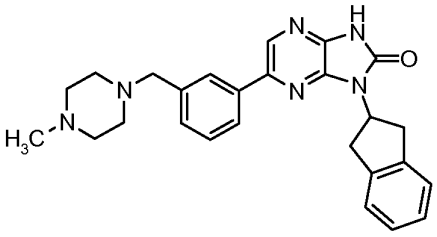
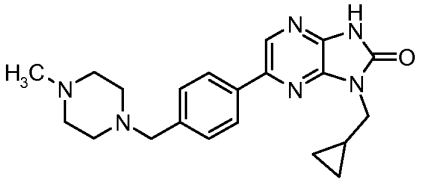
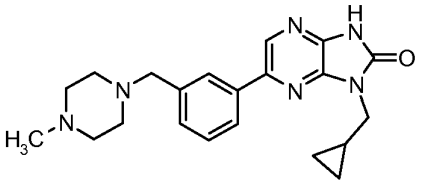
	[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine		phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one

[0441] Examples 224-238 were were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 5.

Table 5.

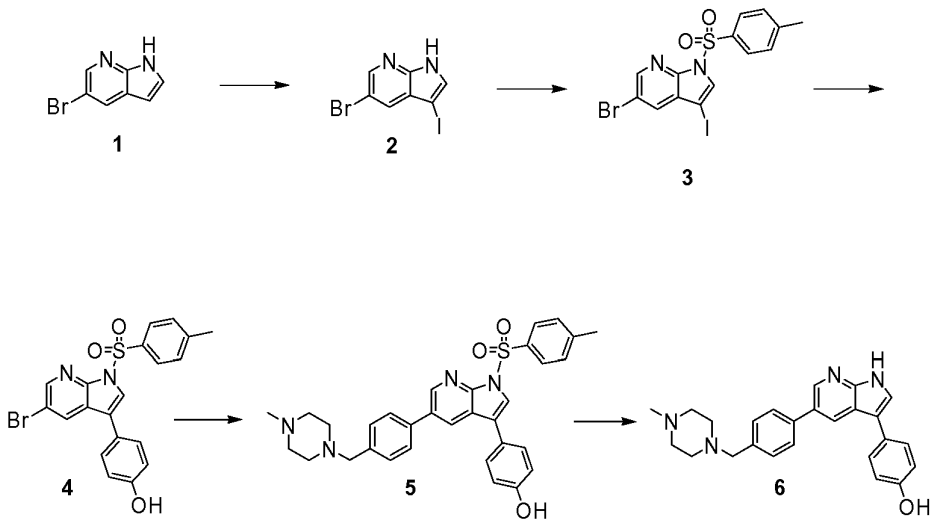
Example	Structure	IUPAC Name	MW
224		1-(2-Methyl-1H-indol-5-yl)-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	453.55
225		1-(1H-Indazol-5-yl)-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	440.51
226		1-(1H-Indol-5-yl)-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	439.52
227		1-(4-Hydroxy-phenyl)-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	416.49

228		1-Benzothiazol-5-yl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	457.56
229		6-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1-phenyl-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	400.49
230		1-(4-Methoxy-phenyl)-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	430.51
231		1-(1H-Indol-5-yl)-6-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	439.52
232		6-(3-Fluoro-4-methanesulfonyl-phenyl)-1-(1H-indol-5-yl)-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	423.43

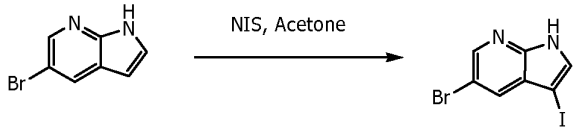
233		6-(3-Fluoro-4-methoxy-phenyl)-1-(1H-indol-5-yl)-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	375.37
235		1-Indan-2-yl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	440.55
236		1-Indan-2-yl-6-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	440.55
237		1-Cyclopropylmethyl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	378.48
238		1-Cyclopropylmethyl-6-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1,3-dihydro-imidazo[4,5-b]pyrazin-2-one	378.48

Examples 234, 239-250,254-259, 264, and 269

Scheme 24

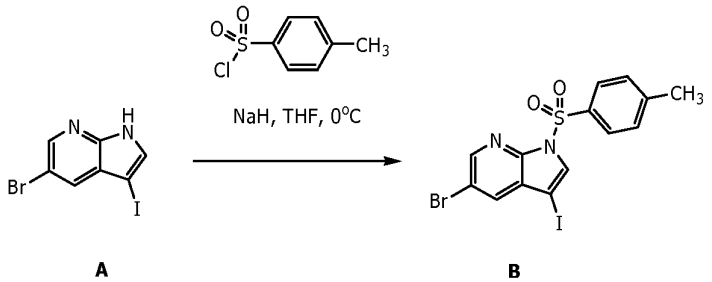


Preparation of 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate A)



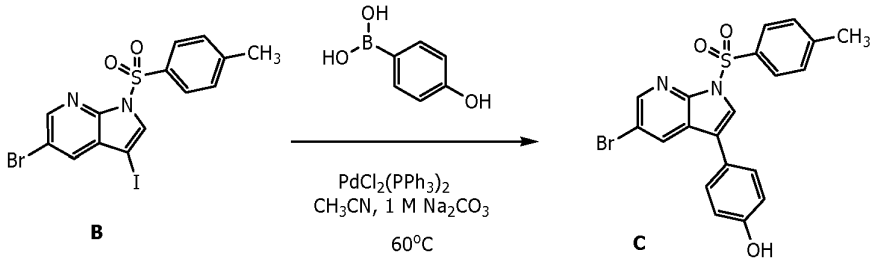
[0442] To a stirred solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (10 g, 50.76 mmol) in 500 mL of acetone N-idodosuccinamide was added and the reaction mixture was stirred for 20 min at room temperature. The product was crashed out as white solid was filtered and washed with 100mL acetone. Resulting solid was dried under vacuum to afford 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (16.34 g, 100%) as a light yellow powder. ^{1}H NMR (DMSO-*d6*, 300MHz) δ 8.51 (d, *J* = 2.1 Hz, 1H), 8.22 (s, 1H), 8.02 (d, *J* = 1.2 Hz, 1 H), 8.00 (d, *J* = 5.1 Hz, 2H), 7.44 (dd, *J* = 8.7 Hz, 0.6 Hz, 2H), 2.35 (s, 3H); MS ESI (m/z): 322/324 $(M+1)^+$, calc. 322.

Preparation of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate B)



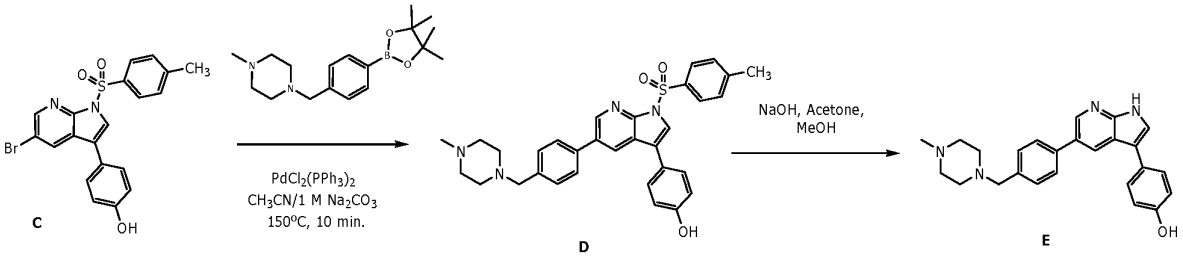
[0443] To a stirred solution of 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (16.82 g, 52.23 mmol) in 522 mL of anhydrous THF cooled to 0°C with an ice bath was added NaH [60% dispersion in mineral oil] (3.76 g, 156.7 mmol). The reaction mixture was stirred for 20 min at 0°C, after which *p*-toluenesulfonyl chloride (14.88 g, 78.3 mmol) was added. The resulting mixture was stirred at 0°C for 1.5 hr, after which cold 0.5 M HCl (20 mL) was added. The mixture was partitioned between EtOAc and 0.5 M HCl, after which the organic layer was separated, dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield a residue that was triturated with 20% CH_2Cl_2 in hexanes to yield the title compound (0.84 g, 81%) as a light yellow powder. ^{1}H NMR (DMSO-*d6*, 300MHz) δ 8.51 (d, *J* = 2.1 Hz, 1H), 8.22 (s, 1H), 8.02 (d, *J* = 1.2 Hz, 1 H), 8.00 (d, *J* = 5.1 Hz, 2H), 7.44 (dd, *J* = 8.7 Hz, 0.6 Hz, 2H), 2.35 (s, 3H); MS ESI (m/z): 477.0/479.0 $(M+1)^+$, calc. 476.

Preparation of 4-[5-Bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-phenol (Intermediate C)



[0444] To a stirred suspension of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.30 g, 0.62 mmol) and 4-hydroxyphenylboronic acid (0.12 mg, 0.75 mmol) in CH_3CN (3 mL) was added 1 M Na_2CO_3 (3 mL) followed by bis(triphenylphosphine)palladium(II) dichloride (0.004 g, 0.062 mmol). The resulting mixture was stirred overnight at 60°C. After the mixture was evaporated to dryness *in vacuo*, it was dissolved in DMF (3 mL), absorbed onto Celite, and dried. The residue was purified via silica gel chromatography using CH_2Cl_2 as the eluent to obtain the title compound (0.26 g, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.48 (d, *J* = 2.1 Hz, 1H), 8.27 (bs, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 8.08 (d, *J* = 8.1 Hz), 7.85 (s, 1H), 7.81 (m, 1H), 7.50 (d, *J* = 8.7 Hz, 1 H), 7.37 (dd, *J* = 1.8, 8.4 Hz), 7.30 (m, 3H), 6.63 (m, 1 H), 2.39 (s, 3H); MS ESI (m/z): 443/445 $(M+1)^+$, calc. 443.31.

Preparation of 4-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol (Compound E, example 242)



[0445] To a solution of 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.220g, 0.5 mmol) in CH_3CN (2.5 mL) in a Personal Chemistry microwave reaction vial was added 1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine (0.20 g, 0.65 mmol), bis(triphenylphosphine)-palladium(II) dichloride (0.003 g, 0.005 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 30 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL) and acetone (2 mL), and 2 M NaOH (1.5 mL) was added. The resulting mixture was stirred at 65°C for 30 min, after which it was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to give a residue purified via preparatory HPLC to give the title compound as a white solid. ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.78 (s, 1H), 11.03 (s, 1 H), 8.51 (d, J = 2.1 Hz, 1H), 8.36 (d, J = 1.8 Hz, 1H), 7.86 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.45 (s, 2H), 7.32 (m, 1H), 6.92 (s, 2H), 6.45 (m, 1 H), 3.85 (s, 6H), 3.70 (s, 3H); HPLC retention time: 2.04 minutes; MS ESI (m/z): 399 $(M+1)^+$, calc. 398.51.

[0446] Using similar procedure described for example 242, the following compounds were prepared by changing boronic acids in the B to C coupling as described in Table 6 unless otherwise indicated.

Table 6.

Example	Boronic Acid	IUPAC Name
234	6-Aminopyridine-3-boronic acid pinacol ester	5-(5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-amine
239	6-Aminopyridine-3-boronic acid pinacol ester for B to C coupling, 1-methyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-	5-{5-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-pyridin-2-ylamine

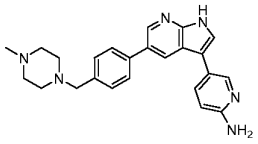
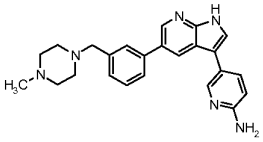
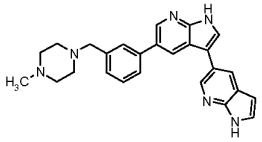
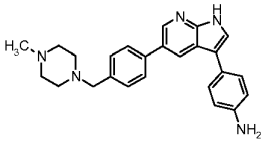
Example	Boronic Acid	IUPAC Name
	dioxaborolan-2-yl)benzyl)piperazine for C to D coupling	
240	7-Azaindole-5-boronic acid pinacol ester	5-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H,1'H-[3,5']bi[pyrrolo[2,3-b]pyridinyl]
241	4-Aminophenyl boronic acid	4-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenylamine
242	4-Hydroxyphenylboronic acid	4-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
243	3-Hydroxyphenylboronic acid	3-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
244	6-Hydroxypyridine-3-boronic acid	5-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-pyridin-2-ol
245	2-Hydroxypyrimidine-5-boronic acid	5-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-pyrimidin-2-ol
246	3-Fluoro-4-hydroxyphenylboronic acid	2-Fluoro-4-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
247	4-Hydroxy-3-methoxyphenylboronic acid	2-Methoxy-4-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
248	3,4-Methylenedioxyphenylboronic acid	3-Benzo[1,3]dioxol-5-yl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine

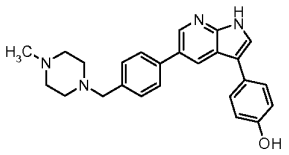
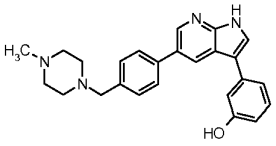
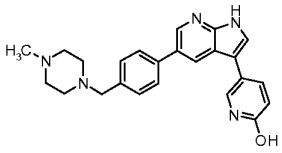
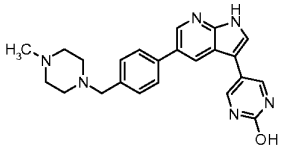
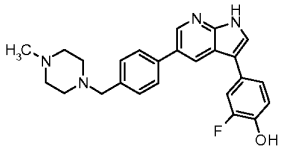
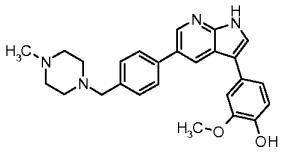
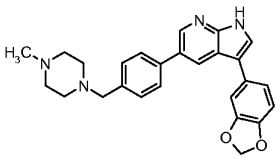
Example	Boronic Acid	IUPAC Name
249	3,6-Dihydro-2H-pyridine-1-N-Boc-4-boronic acid, pinacol ester	4-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester
250	1,2,3,6-Tetrahydropyridine-4-yl-boronic acid pinacol ester hydrochloride	5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridine
254	4-Fluoro-3-hydroxyphenylboronic acid	2-Fluoro-5-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
255	3-Hydroxy-4-methoxyphenylboronic acid	2-Methoxy-5-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
256	4-Hydroxy-2-methylphenylboronic acid	3-Methyl-4-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
257	5-Hydroxy-2-methoxyphenylboronic acid	4-Methoxy-3-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
258	3-Aminocarbonylphenylboronic acid	3-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide
259	3-(N-Methylaminocarbonyl)phenylboronic acid	N-Methyl-3-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide
264	3-Hydroxy-4-methylphenylboronic acid	2-Methyl-5-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol

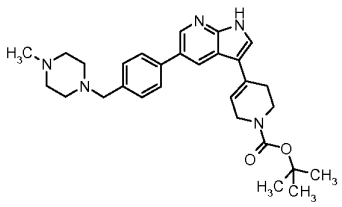
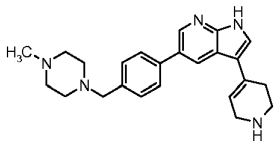
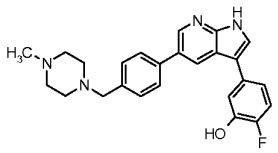
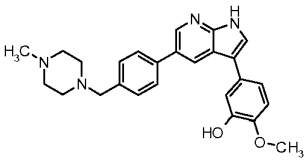
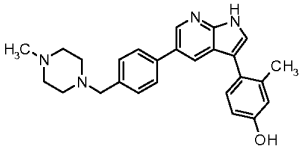
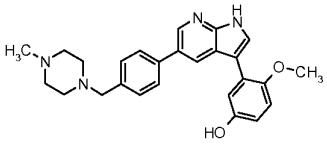
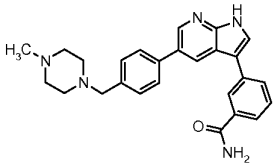
Example	Boronic Acid	IUPAC Name
269	1H-indol-5-ylboronic acid for B to C coupling; 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine for C to D coupling	3-(1H-indol-5-yl)-5-(4-(1-methylpiperidin-4-yloxy)phenyl)-1H-pyrrolo[2,3-b]pyridine

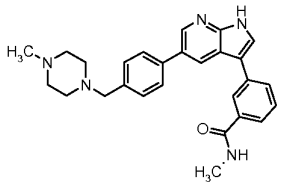
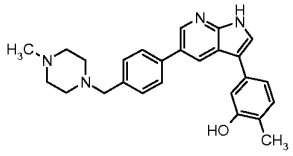
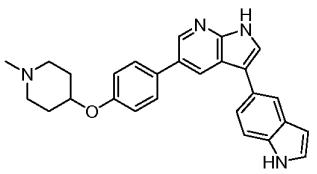
[0447] Examples 242-264 were were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 7.

Table 7.

Example	Structure	IUPAC Name	MW
234		5-(5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-amine	398.50
239		5-{5-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-pyridin-2-ylamine	398.50
240		5-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H,1'H-[3,5']bi[pyrrolo[2,3-b]pyridinyl]	422.52
241		4-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenylamine	397.52

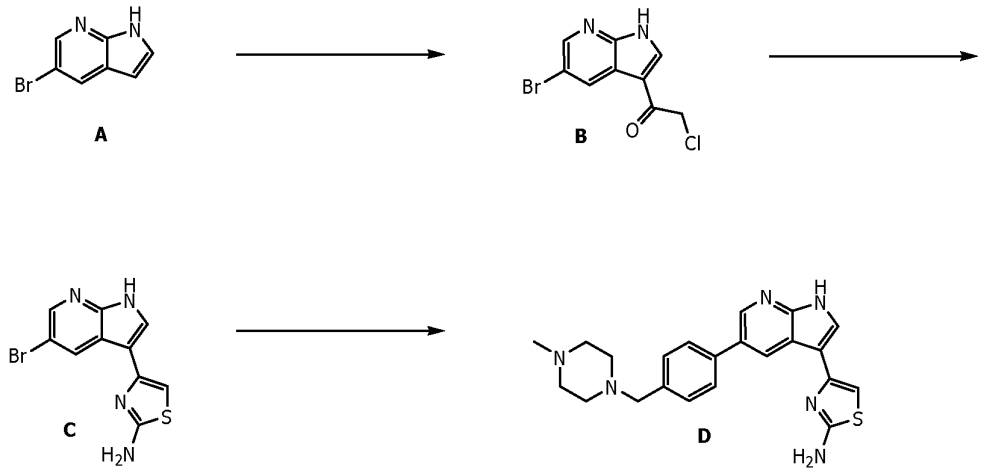
242		4-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	398.51
243		3-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	398.51
244		5-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-pyridin-2-ol	399.5
245		5-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-pyrimidin-2-ol	400.49
246		2-Fluoro-4-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	416.5
247		2-Methoxy-4-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	428.54
248		3-Benzo[1,3]dioxol-5-yl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine	426.52

249		4-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester	487.65
250		5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridine	387.53
254		2-Fluoro-5-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	416.5
255		2-Methoxy-5-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	428.54
256		3-Methyl-4-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	412.54
257		4-Methoxy-3-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	428.54
258		3-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide	425.54

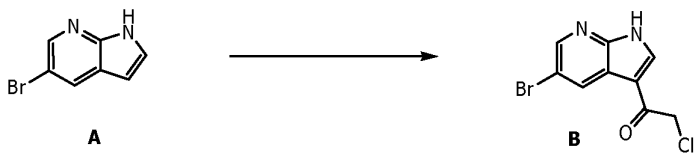
259		N-Methyl-3-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-benzamide	439.57
264		2-Methyl-5-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	412.54
269		3-(1H-indol-5-yl)-5-(4-(1-methylpiperidin-4-yloxy)phenyl)-1H-pyrrolo[2,3-b]pyridine	422.52

Example 260

Scheme 25



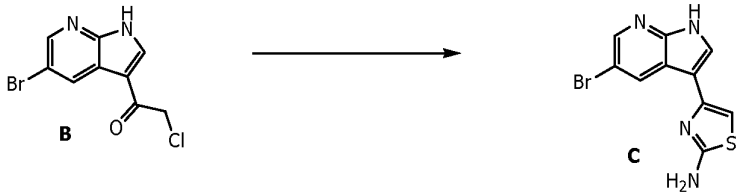
Preparation of 1-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-chloro-ethanone



[0448] To a suspension of $AlCl_3$ (3.38g, 25.38mmol) in dichloromethane (100mL) was added 5-Bromo-1H-pyrrolo[2,3-b]pyridine (1g, 5.07 mmol). After stirring for 30 min,

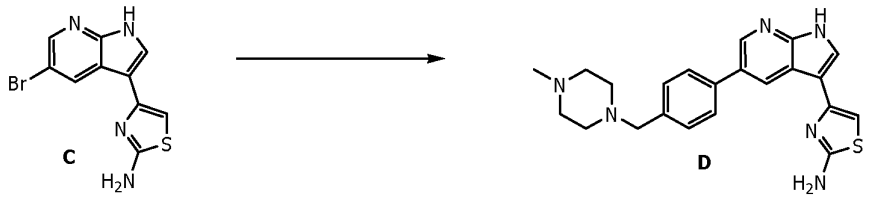
chloroacetyl chloride (2.84g, 25.38 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. On completion, sovents were evaporated and quenched with aq. $NaHCO_3$ solution at 0 °C. Resulting mixture was extracted with EtOAc. The organic layer was dried over Na2SO4 and filtered through a plug of silica gel. Solvent was evaporated to dryness to give 1-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-chloro-ethanone (1.3g, 93% yield).

Preparation of 4-(5-Bromo-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine



[0449] A solution 1-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-chloro-ethanone (0.32g, 1.17 mmol) and thio urea (0.097g, 1.28 mmol) in ethanol (4mL) was stirred at 80 °C for 1.5 hours. The resulting precipitate was filtered, washed with MeOH, and dried under vacuum to give 4-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine (0.34g, 99% yield).

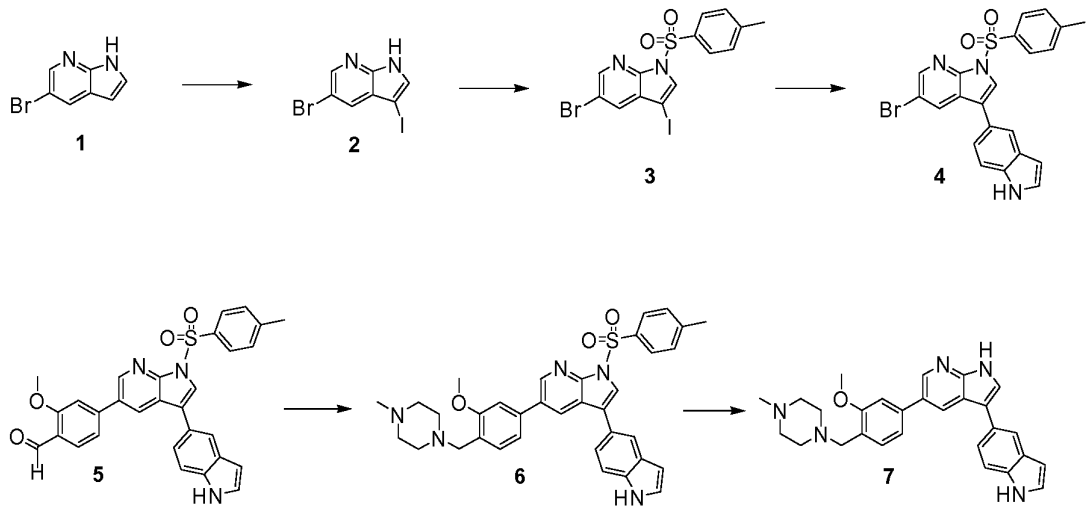
Preparation of 4-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-thiazol-2-ylamine



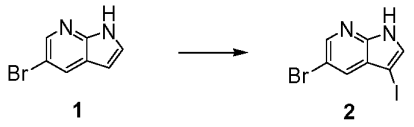
[0450] In a personal chemistry microwave reaction vial 4-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine (0. 2g, 0.67 mmol) and 1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine (0.23 g, 0.74 mmol), bis(triphenylphosphine)-palladium(II) dichloride (0.004 g, 0.006 mmol) in acetonitrile (2mL), and 1 M Na_2CO_3 (2 mL) were added. The resulting mixture was de-gassed with N_2 for 10 min, after which it was heated at 175°C for 30 min in a Personal Chemistry Optimizer. The mixture was diluted with DMF (3mL), and concentrated *in vacuo* and purified on silica gel column using dichloromethane and methanol to afford 4-{5-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-thiazol-2-ylamine.

Examples 262 and 263

Scheme 26

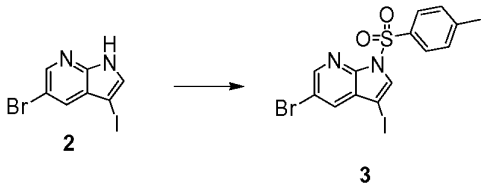


Preparation of 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate 2)



[0451] To a stirred solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (10 g, 50.76 mmol) in 500 mL of acetone N-idodosuccinamide was added and the reaction mixture was stirred for 20 min at room temperature. The product was crashed out as white solid was filtered and washed with 100mL acetone. Resulting solid was dried under vacuum to afford 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (16.34 g, 100%) as a light yellow powder. ^{1}H NMR (DMSO-*d6*, 300MHz) δ 8.51 (d, *J* = 2.1 Hz, 1H), 8.22 (s, 1H), 8.02 (d, *J* = 1.2 Hz, 1 H), 8.00 (d, *J* = 5.1 Hz, 2H), 7.44 (dd, *J* = 8.7 Hz, 0.6 Hz, 2H), 2.35 (s, 3H); MS ESI (m/z): 322/324 $(M+1)^+$, calc. 322.

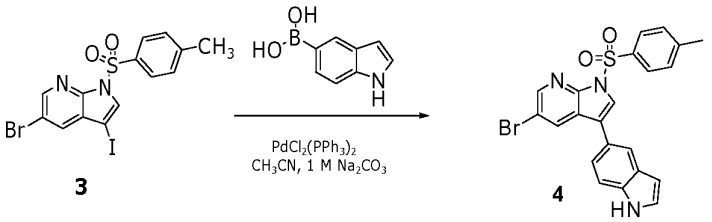
Preparation of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate 3)



[0452] To a stirred solution of 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (16.82 g, 52.23 mmol) in 522 mL of anhydrous THF cooled to 0°C with an ice bath was added NaH [60% dispersion in mineral oil] (3.76 g, 156.7 mmol). The reaction mixture was stirred for 20 min at 0°C, after which *p*-toluenesulfonyl chloride (14.88 g, 78.3 mmol) was added. The resulting mixture was stirred at 0°C for 1.5 hr, after which cold 0.5 M HCl (20 mL) was added. The mixture was partitioned between EtOAc and 0.5 M HCl, after which the organic layer was

separated, dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield a residue that was triturated with 20% CH_2Cl_2 in hexanes to yield the title compound (0.84 g, 81%) as a light yellow powder. ^{1}H NMR (DMSO-*d6*, 300MHz) δ 8.51 (d, *J* = 2.1 Hz, 1H), 8.22 (s, 1H), 8.02 (d, *J* = 1.2 Hz, 1 H), 8.00 (d, *J* = 5.1 Hz, 2H), 7.44 (dd, *J* = 8.7 Hz, 0.6 Hz, 2H), 2.35 (s, 3H); MS ESI (m/z): 477.0/479.0 $(M+1)^+$, calc. 476.

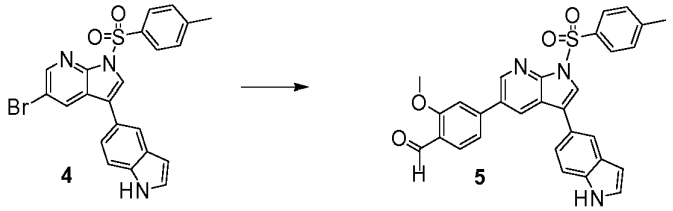
Preparation of 4-[5-Bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-phenol (Intermediate 4)



3 4

[0453] To a stirred suspension of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.66 g, 5.57 mmol) and 1*H*-indol-5-ylboronic acid (0.89 g, 5.57 mmol) in CH_3CN (36 mL) was added 1 M Na_2CO_3 (18 mL) followed by bis(triphenylphosphine)palladium(II) dichloride (0.20 g, 0.275 mmol). The resulting mixture was stirred overnight at 60°C. After the mixture was evaporated to dryness *in vacuo*, it was dissolved in DMF (3 mL), absorbed onto Celite, and dried. The residue was purified via silica gel chromatography using CH_2Cl_2 as the eluent to obtain the title compound (1.65 g, 63%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.48 (d, *J* = 2.1 Hz, 1H), 8.27 (bs, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 8.08 (d, *J* = 8.1 Hz), 7.85 (s, 1H), 7.81 (m, 1H), 7.50 (d, *J* = 8.7 Hz, 1 H), 7.37 (dd, *J* = 1.8, 8.4 Hz), 7.30 (m, 3H), 6.63 (m, 1 H), 2.39 (s, 3H); MS ESI (m/z): 466.2/468.2 $(M+1)^+$, calc. 465.

Preparation of 4-[3-(1H-Indol-5-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-methoxy-benzaldehyde (Intermediate 5)

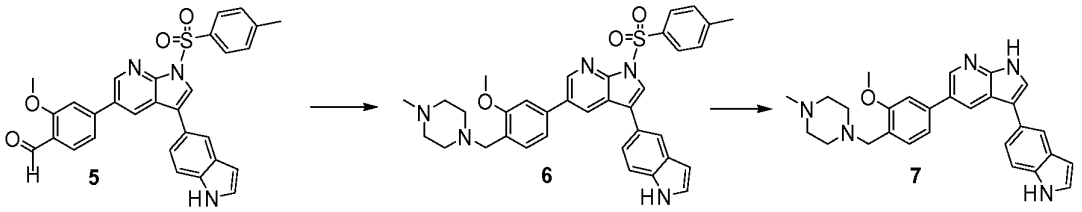


4 5

[0454] To a solution of 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.100 g, 0.21 mmol) in CH_3CN (1 mL) in a Personal Chemistry microwave reaction vial was added 1-2-methoxy-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (0.042 g, 0.25 mmol), bis(triphenylphosphine)-palladium(II) dichloride (0.02 g, 0.002 mmol), and 1 M Na_2CO_3 (1 mL).

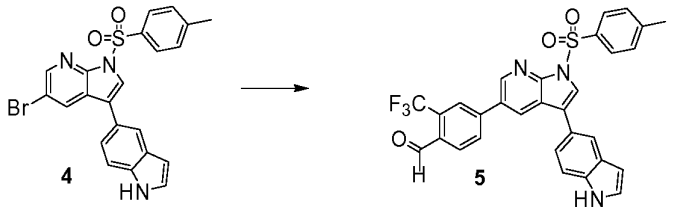
The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 30 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue purified on silica gel column to give 4-[3-(1H-Indol-5-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-methoxy-benzaldehyde (0.66g, 59% yield). MS ESI (m/z): 521/523 $(M+1)^+$, calc. 521.51.

Preparation of 3-(1H-Indol-5-yl)-5-[3-methoxy-4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine (Compound 262)



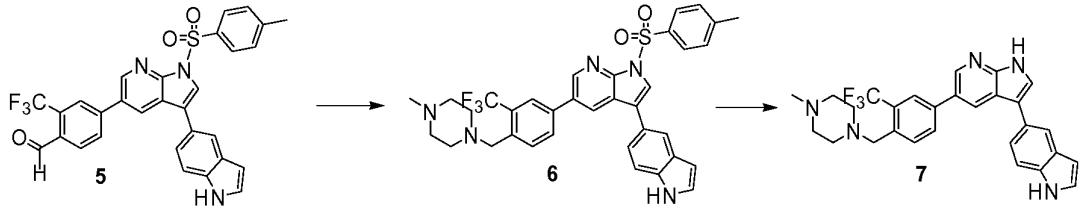
[0455] To a solution of 4-[3-(1H-Indol-5-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-methoxy-benzaldehyde (0.066 g, 0.128 mmol) in CH_2Cl_2 (3 mL) was added 1-methylpiperazine (22 mL, 0.19 mmol) and sodium triacetoxyborohydride (81 mg, 0.38 mmol). The reaction mixture was stirred for 1 hr at room temperature, after which it was partitioned between CH_2Cl_2 and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in 3:2 MeOH:acetone (5 mL), and 2 M NaOH (1.5 mL) was added. The resulting mixture was stirred at 65°C for 30 min, after which it was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to provide a residue that was subjected to preparatory HPLC to yield 3-(1H-Indol-5-yl)-5-[3-methoxy-4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine (0.037g, 63% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 11.81 (s, 1H), 11.06 (s, 1H), 8.55 (d, J = 2.1 Hz, 1H), 8.40 (d, J = 2.4 Hz, 1H), 7.88 (d, J = 1.6 Hz, 1H), 7.74 (d, J = 1.6 Hz, 1H), 7.46 (s, 2H), 7.37 (dd, J = 6.4 Hz, 1H), 7.35 (d, J = 6.4 Hz, 1H), 7.26 (dd, J = 1.8, 6.4 Hz, 2H)), 6.46 (s, 1H), 3.86 (d, J = 1.2 Hz, 2H), 3.32 (s, 3H), 2.49-42 (m, 8H), 2.13 (s, 3H);; MS ESI (m/z) 452 $(M+1)^+$, calc. 451.56.

Preparation of 4-[3-(1H-Indol-5-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-trifluoromethyl-benzaldehyde



[0456] To a solution of 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.100g, 0.21 mmol) in CH_3CN (1 mL) in a Personal Chemistry microwave reaction vial was added 1-2-trifluromethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (0.056 g, 0.25 mmol), bis(triphenylphosphine)-palladium(II) dichloride (0.020 g, 0.028 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 30 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue purified via preparatory HPLC to give 4-[3-(1H-Indol-5-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-trifluoromethyl-benzaldehyde as a white solid. MS ESI (m/z): 551/553 $(M+1)^+$, calc. 551.63.

Preparation of 3-(1H-Indol-5-yl)-5-[3-methoxy-4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine (Compound 263)

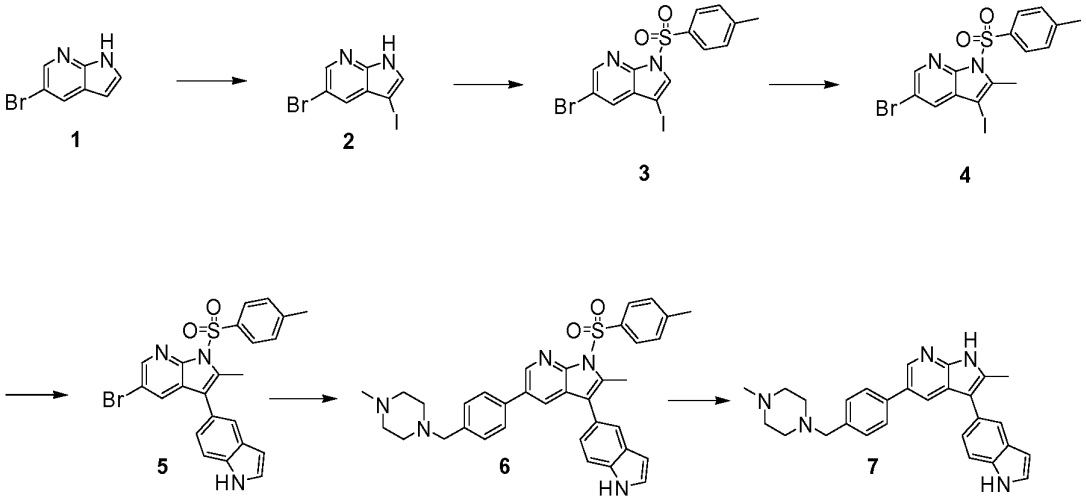


[0457] To a solution of 4-[3-(1H-indol-5-yl)-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-trifluoromethyl-benzaldehyde (0.12 g, 0.214 mmol) in CH_2Cl_2 (3 mL) was added 1-methylpiperazine (32 mL, 0.32 mmol) and sodium triacetoxyborohydride (136 mg, 0.64 mmol). The reaction mixture was stirred for 1 hr at room temperature, after which it was partitioned between CH_2Cl_2 and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in 3:2 MeOH:acetone (5 mL), and 2 M NaOH (1.5 mL) was added. The resulting mixture was stirred at 65°C for 30 min, after which it was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to provide a residue that was subjected to silica gel column to yield 3-(1H-indol-5-yl)-5-[4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-1H-pyrrolo[2,3-b]pyridine (0.024 g, 24% yield) . ^1H NMR ($CDCl_3$, 400 MHz): δ 11.89 (s, 1H),

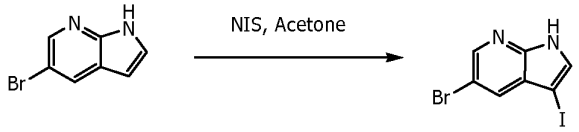
11.07 (s, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 1.6 Hz, 1H), 7.89 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.46 (dd, J = 1.8, 6.4 Hz, 2H)), 7.34 (d, J = 2.4 Hz, 1H), 6.46 (s, 1H), 3.63 (s, 2H), 3.32 (s, 3H), 2.49-42 (m, 8H), 2.14 (s, 3H);; MS ESI (m/z) 490 $(M+1)^+$, calc. 489.53.

Example 217

Method A: Synthesis of 2-Methylazaindole Derivatives



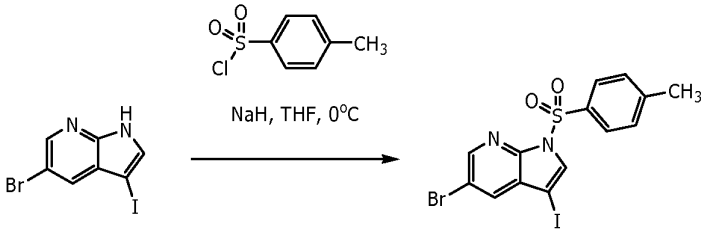
Preparation of 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate A)



A

[0458] To a stirred solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (10 g, 50.76 mmol) in 500 mL of acetone N-idodosuccinamide was added and the reaction mixture was stirred for 20 min at room temperature. The product was crashed out as white solid was filtered and washed with 100mL acetone. Resulting solid was dried under vacuum to afford 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (16.34 g, 100%) as a light yellow powder. ^{1}H NMR (DMSO-*d6*, 300MHz) δ 8.51 (d, J = 2.1 Hz, 1H), 8.22 (s, 1H), 8.02 (d, J = 1.2 Hz, 1 H), 8.00 (d, J = 5.1 Hz, 2H), 7.44 (dd, J = 8.7 Hz, 0.6 Hz, 2H), 2.35 (s, 3H); MS ESI (m/z): 322/324 $(M+1)^+$, calc. 322.

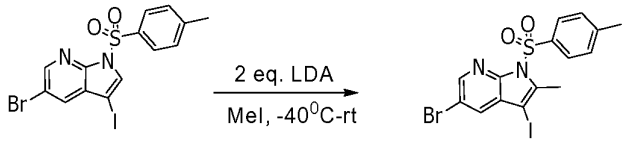
Preparation of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate B)



A B

[0459] To a stirred solution of 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (16.82 g, 52.23 mmol) in 522 mL of anhydrous THF cooled to 0°C with an ice bath was added NaH [60% dispersion in mineral oil] (3.76 g, 156.7 mmol). The reaction mixture was stirred for 20 min at 0°C, after which *p*-toluenesulfonyl chloride (14.88 g, 78.3 mmol) was added. The resulting mixture was stirred at 0°C for 1.5 hr, after which cold 0.5 M HCl (20 mL) was added. The mixture was partitioned between EtOAc and 0.5 M HCl, after which the organic layer was separated, dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield a residue that was triturated with 20% CH_2Cl_2 in hexanes to yield the title compound (0.84 g, 81%) as a light yellow powder. ^{1}H NMR (DMSO-*d6*, 300MHz) δ 8.51 (d, *J* = 2.1 Hz, 1H), 8.22 (s, 1H), 8.02 (d, *J* = 1.2 Hz, 1 H), 8.00 (d, *J* = 5.1 Hz, 2H), 7.44 (dd, *J* = 8.7 Hz, 0.6 Hz, 2H), 2.35 (s, 3H); MS ESI (m/z): 477.0/479.0 $(M+1)^+$, calc. 476.

Preparation of Method A Intermediate 3: 5-Bromo-3-iodo-2-methyl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine

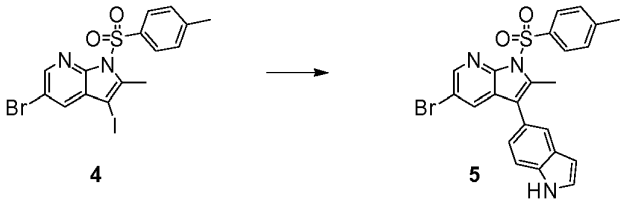


B C

[0460] To a solution of diisopropylamine (2.8 eq, 1.66 mmol, 240 µL) in THF (2 ml) at -10°C is added *n*-butyllithium (1.6 M in hexane, 2.6 eq, 1.54 mmol, 965 µL) dropwise. The mixture is allowed to stir for 30 min and then cooled to -40°C. A solution of compound **2** (1 eq., 200 mg, 0.593 mmol) in THF is added dropwise and the mixture is stirred for 30 min at -35°C. Iodomethane (3 eq, 1.78 mmol, 111 µL) is added in a dropwise fashion and the mixture is stirred for 2 h while warming up to room temperature. The reaction is quenched by addition of a saturated NH_4Cl solution, extracted with EtOAc and purified by silica gel chromatography (stepwise gradient of 0 to 15% EtOAc in hexane). 126 mg (0.359 mmol, 60%) of compound **3** are obtained. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.37 (d, *J* = 2.4 Hz, 1H), 8.12 (m, 2 H), 7.81 (d, *J* =

2.4 Hz, 1H), 7.58 (m, 1H), 7.50 (m, 2H), 6.24 (d, J = 1.2 Hz, 1H), 2.73 (d, J = 1.2 Hz, 3H). MS (m/z): 352 (M+H).

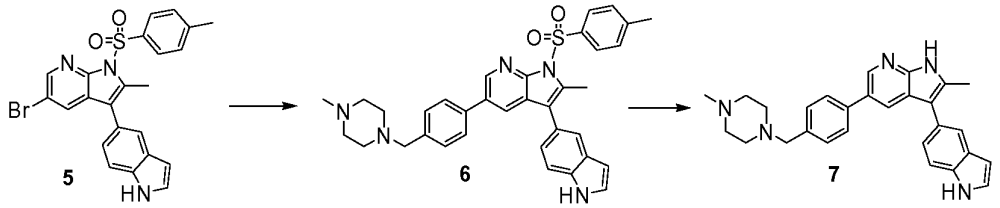
Preparation of 4-[5-Bromo-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-phenol (Intermediate C)



4 5

[0461] To a stirred suspension of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.30 g, 0.62 mmol) and 1*H*-indol-5-ylboronic acid (0.12 mg, 0.75 mmol) in CH_3CN (3 mL) was added 1 M Na_2CO_3 (3 mL) followed by bis(triphenylphosphine)palladium(II) dichloride (0.004 g, 0.062 mmol). The resulting mixture was stirred overnight at 60°C. After the mixture was evaporated to dryness *in vacuo*, it was dissolved in DMF (3 mL), absorbed onto Celite, and dried. The residue was purified via silica gel chromatography using CH_2Cl_2 as the eluent to obtain the title compound (0.26 g, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.48 (d, J = 2.1 Hz, 1H), 8.27 (bs, 1H), 8.26 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 8.1 Hz), 7.85 (s, 1H), 7.81 (m, 1H), 7.50 (d, J = 8.7 Hz, 1 H), 7.37 (dd, J = 1.8, 8.4 Hz), 7.30 (m, 3H), 6.63 (m, 1 H), 2.39 (s, 3H); MS ESI (m/z): 466.2/468.2 $(M+1)^+$, calc. 465.

Preparation of 3-(1H-Indol-5-yl)-2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridine (Compound E, example 217)



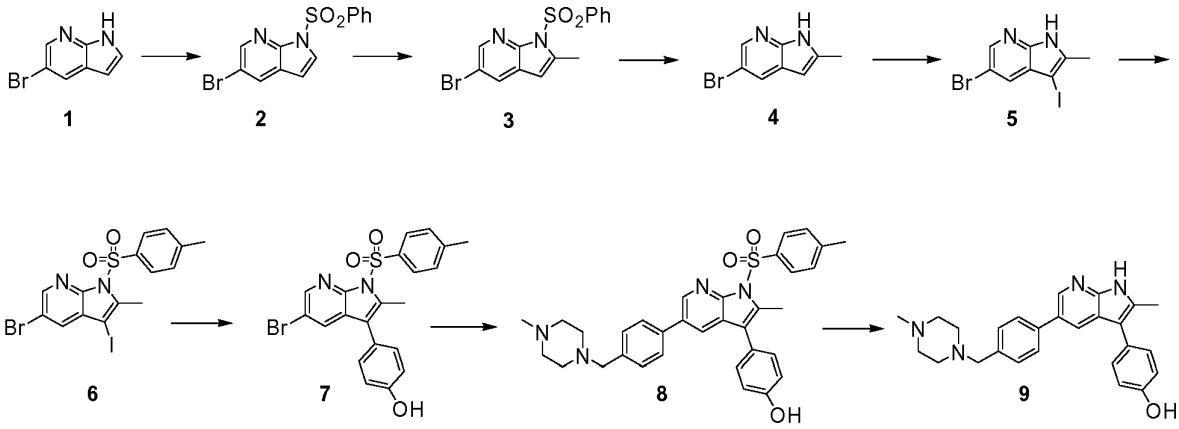
5 6 7

[0462] To a solution of 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.220g, 0.5 mmol) in CH_3CN (2.5 mL) in a Personal Chemistry microwave reaction vial was added 1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine (0.20 g, 0.65 mmol), bis(triphenylphosphine)-palladium(II) dichloride (0.003 g, 0.005 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 30 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL) and acetone (2

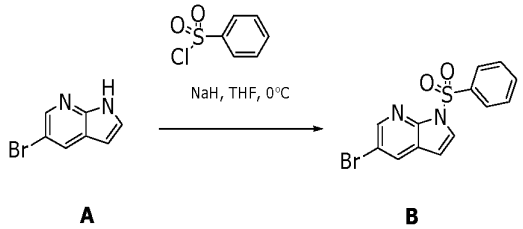
mL), and 2 M NaOH (1.5 mL) was added. The resulting mixture was stirred at 65°C for 30 min, after which it was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to give a residue purified via preparatory HPLC to give the title compound as a white solid. ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.78 (s, 1H), 11.03 (s, 1 H), 8.51 (d, *J* = 2.1 Hz, 1H), 8.36 (d, *J* = 1.8 Hz, 1H), 7.86 (s, 1H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.45 (s, 2H), 7.32 (m, 1H), 6.92 (s, 2H), 6.45 (m, 1 H), 3.85 (s, 6H), 3.70 (s, 3H); HPLC retention time: 2.04 minutes; MS ESI (m/z): 399 $(M+1)^+$, calc. 398.51.

Examples 265-266, 268, 270-274

Method B: Synthesis of 2-Methylazaindole Derivatives

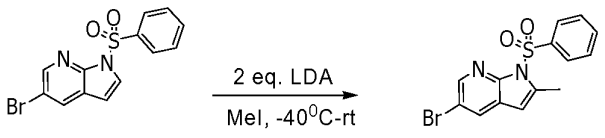


Preparation of Method A Intermediate 2: 1-Benzenesulfonyl-5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine



[0463] 5-Bromoazaindole (**1**, 2.00 g, 10.1 mmol), tetrabutylammonium bromide (0.03 eq, 0.25 mmol, 82 mg) and powdered NaOH (3 eq, 30.45 mmol, 1.22 g) are combined in DCM (100 ml) and cooled to 0°C. Phenylsulfonyl chloride (1.25 eq, 12.69 mmol, 1.62 mL) is added dropwise. After the addition is completed the mixture is stirred for 2h at 0°C. The mixture is filtered, absorbed on Celite and purified by silica gel chromatography with a 40 to 60% gradient of EtOAc in hexane. 2.58 g (7.65 mmol, 75% yield) of **2** is obtained. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.45 (d, *J* = 1.8 Hz, 1H), 8.17 (m, 2 H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.74 (d, *J* = 3.9 Hz, 1H), 7.60 (m, 1H), 7.50 (m, 2H), 6.55 (d, *J* = 3.9 Hz, 1H). MS (m/z): 338 (M+H).

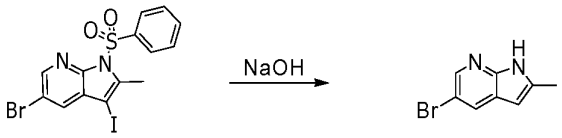
Preparation of Method A Intermediate 3: 1-Benzenesulfonyl-5-bromo-2-methyl-1H-pyrrolo[2,3-b]pyridine



B C

[0464] To a solution of diisopropylamine (2.8 eq, 1.66 mmol, 240 μL) in THF (2 ml) at -10°C is added *n*-butyllithium (1.6 M in hexane, 2.6 eq, 1.54 mmol, 965 l) dropwise. The mixture is allowed to stir for 30 min and then cooled to -35°C. A solution of compound **2** (1 eq., 200 mg, 0.593 mmol) in THF is added dropwise and the mixture is stirred for 30 min at -35°C. Iodomethane (3 eq, 1.78 mmol, 111 μL) is added in a dropwise fashion and the mixture is stirred for 2 h while warming up to room temperature. The reaction is quenched by addition of a saturated NH_4Cl solution, extracted with EtOAc and purified by silica gel chromatography (stepwise gradient of 0 to 15% EtOAc in hexane). 126 mg (0.359 mmol, 60%) of compound **3** are obtained. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.37 (d, J = 2.4 Hz, 1H), 8.12 (m, 2 H), 7.81 (d, J = 2.4 Hz, 1H), 7.58 (m, 1H), 7.50 (m, 2H), 6.24 (d, J = 1.2 Hz, 1H), 2.73 (d, J = 1.2 Hz, 3H). MS (m/z): 352 (M+H).

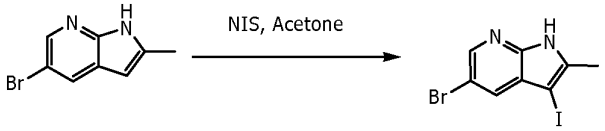
Preparation of Method A Intermediate 4: 5-Bromo-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine



C D

[0465] Starting material **3** (88 mg, 0.251 mmol) is dissolved in MeOH (4 ml), 2 N NaOH (1 ml) is added and the mixture is refluxed for 2 h. EtOAc is added and the organic phase is washed with 1 N NaOH and water. After purification by silica gel chromatography (slow gradient from 0 to 2% MeOH in DCM), 40 mg (0.19 mmol, 76%) of **4** is obtained. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.26 (bs, 1H), 8.22 (d, J = 2.1 Hz, 1H), 8.92 (d, J = 2.1 Hz, 1H), 6.13 (s, 1H), 2.52 (s, 3H). MS (m/z): 210 (M+H).

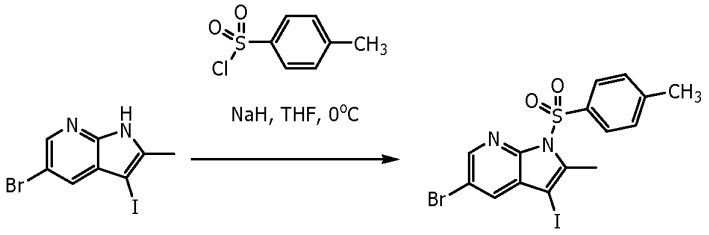
Preparation of Method A Intermediate 5: 5-Bromo-3-iodo-2-methyl-1H-pyrrolo[2,3-b]pyridine



A

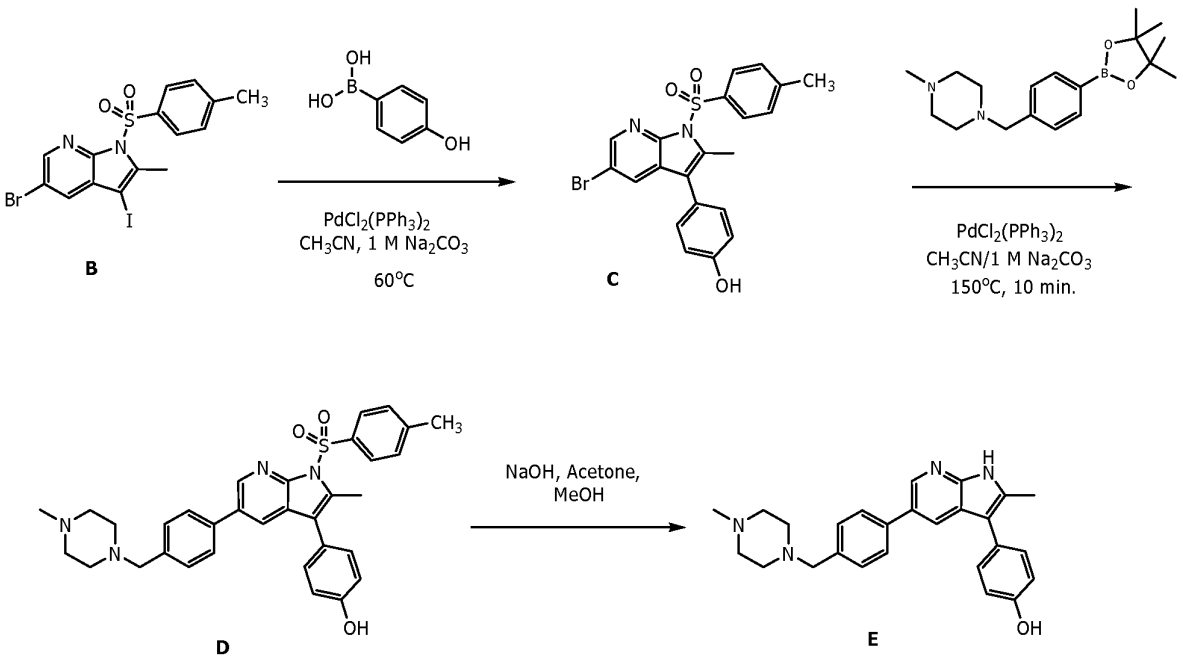
[0466] A mixture of **4** (85 mg, 0.378 mmol) and N-iodosuccinimide (1.1 eq, 0.42 mmol, 95 mg) in acetone (1.5 ml) is stirred for 1 h at room temperature. The precipitate is filtered off, washed with cold acetone and dried to yield 90 mg (0.267 mmol, 71 %) of the desired product.

Preparation of Method A Intermediate 6: 1-Benzenesulfonyl-5-bromo-3-iodo-2-methyl-1H-pyrrolo[2,3-b]pyridine

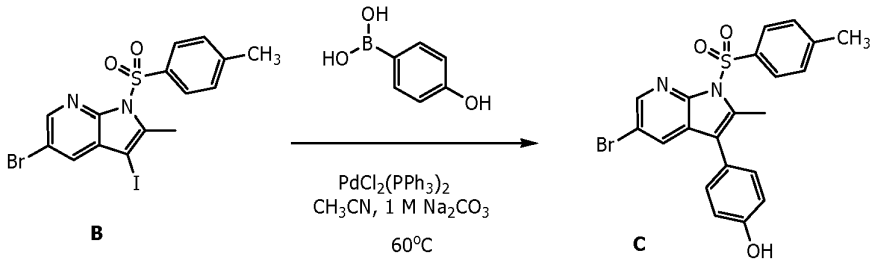


A B

[0467] Compound **5** (90 mg, 0.267 mmol), tetrabutylammonium bromide (0.025 eq, 0.0067 mmol, 3 mg) and powdered NaOH (3 eq, 0.8 mmol, 32 mg) are combined in DCM (3 ml) and cooled to 0°C. Phenylsulfonyl chloride (1.25 eq, 0.334 mmol, 43 l) is added dropwise. After the addition is completed the mixture is stirred for 15 min at 0°C and then allowed to warm up to room temperature over 2h. The mixture is filtered, absorbed on Celite and purified by silica gel chromatography eluting with DCM. 112 mg (0.235 mmol, 88% yield) of **6** is obtained.



Preparation of 4-[5-Bromo-2-methyl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-phenol (Intermediate C)



[0468] To a stirred suspension of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine `(0.30 g, 0.62 mmol) and 1*H*-indol-5-ylboronic acid (0.12 mg, 0.75 mmol) in CH_3CN (3 mL) was added 1 M Na_2CO_3 (3 mL) followed by bis(triphenylphosphine)palladium(II) dichloride (0.004 g, 0.062 mmol). The resulting mixture was stirred overnight at 60°C. After the mixture was evaporated to dryness *in vacuo*, it was dissolved in DMF (3 mL), absorbed onto Celite, and dried. The residue was purified via silica gel chromatography using CH_2Cl_2 as the eluent to obtain the title compound (0.26 g, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.48 (d, J = 2.1 Hz, 1H), 8.27 (bs, 1H), 8.26 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 8.1 Hz), 7.85 (s, 1H), 7.81 (m, 1H), 7.50 (d, J = 8.7 Hz, 1 H), 7.37 (dd, J = 1.8, 8.4 Hz), 7.30 (m, 3H), 6.63 (m, 1 H), 2.39 (s, 3H); MS ESI (m/z): 466.2/468.2 $(M+1)^+$, calc. 465.

Preparation of 4-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol (Compound E, example 266)

[0469] To a solution of 5-bromo-3-(1*H*-indol-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.220g, 0.5 mmol) in CH_3CN (2.5 mL) in a Personal Chemistry microwave reaction vial was added 1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine (0.20 g, 0.65 mmol), bis(triphenylphosphine)-palladium(II) dichloride (0.003 g, 0.005 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 30 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL) and acetone (2 mL), and 2 M NaOH (1.5 mL) was added. The resulting mixture was stirred at 65°C for 30 min, after which it was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to give a residue purified via preparatory HPLC to give the title compound as a white solid. ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 11.78 (s, 1H), 11.03 (s, 1 H), 8.51 (d, J = 2.1 Hz, 1H), 8.36 (d, J = 1.8 Hz, 1H), 7.86 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.45 (s, 2H), 7.32 (m, 1H), 6.92 (s, 2H), 6.45 (m, 1 H), 3.85 (s, 6H), 3.70 (s, 3H); HPLC retention time: 2.04 minutes; MS ESI (m/z): 399 $(M+1)^+$, calc. 398.51.

[0470] Using similar procedure described for example 266, the following compounds were prepared by changing boronic acids described in Table 8.

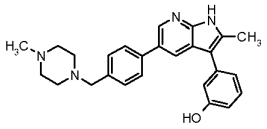
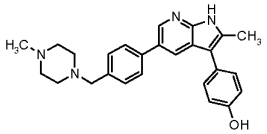
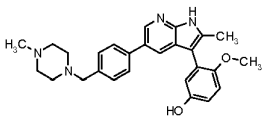
Table 8.

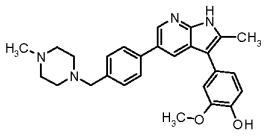
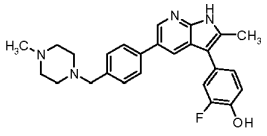
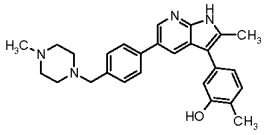
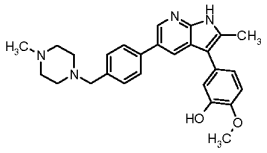
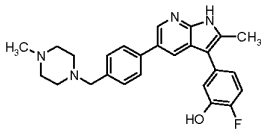
Example	Boronic Acid	IUPAC Name
265	3-Hydroxyphenylboronic acid	3-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
266	4-Hydroxyphenylboronic acid	4-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
268	5-Hydroxy-2-methoxyphenylboronic acid	4-Methoxy-3-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
270	4-Hydroxy-3-methoxyphenylboronic acid	2-Methoxy-4-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol

Example	Boronic Acid	IUPAC Name
271	3-Fluoro-4-hydroxyphenylboronic acid	2-Fluoro-4-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
272	3-Hydroxy-4-methylphenylboronic acid	2-Methyl-5-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
273	3-Hydroxy-4-methoxyphenylboronic acid	2-Methoxy-5-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol
274	4-Fluoro-3-hydroxyphenylboronic acid	2-Fluoro-5-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol

[0471] Examples 265-274 were physically characterized by electro spray ionization mass spectrometry. Structures and molecular masses are given below in Table 9.

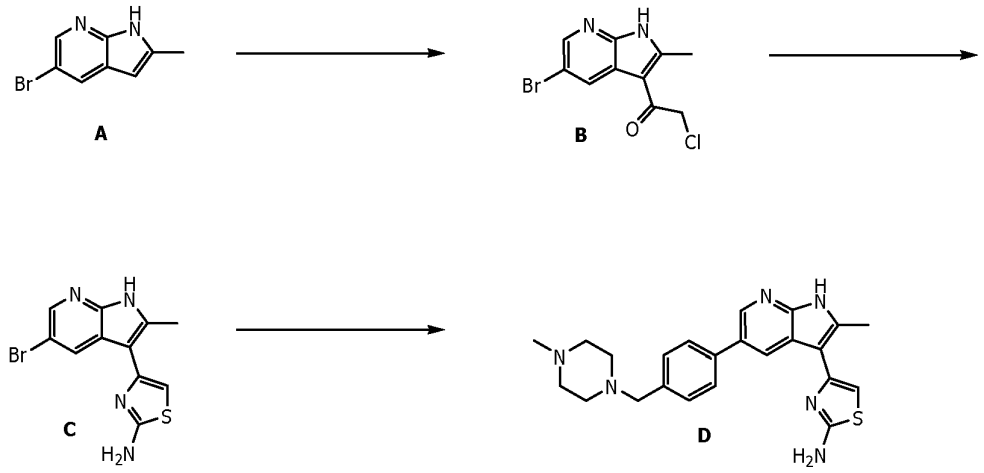
Table 9.

Example	Structure	IUPAC Name	MW
265		3-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	412.54
266		4-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	412.54
268		4-Methoxy-3-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	442.57

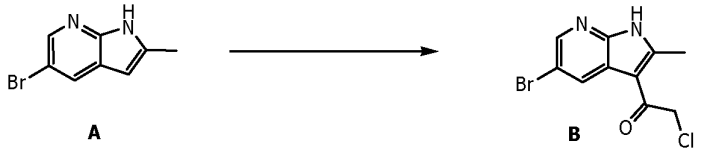
270		2-Methoxy-4-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	442.57
271		2-Fluoro-4-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	430.53
272		2-Methyl-5-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	426.57
273		2-Methoxy-5-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	442.57
274		2-Fluoro-5-{2-methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-phenol	430.53

Example 267

Scheme 27

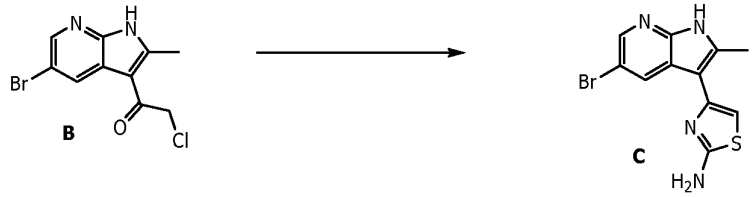


Preparation of 1-(5-Bromo-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-chloro-ethanone



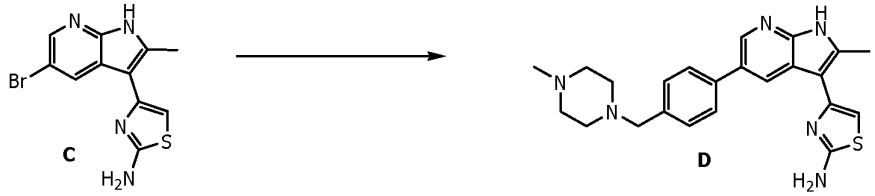
[0472] To a suspension of $AlCl_3$ (1.57g, 11.84mmol) in dichloromethane (50mL) was added 5-Bromo-2-methyl-1H-pyrrolo[2,3-b]pyridine. After stirring for 30 min, chloroacetyl chloride (1.33g, 11.84 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. On completion, solvents were evaporated and quenched with aq. NaHCO3 solution at 0 °C. Resulting mixture was extracted with EtOAc. The organic layer was dried over Na2SO4 and filtered through a plug of silica gel. Solvent was evaporated to dryness to give 1-(5-Bromo-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-chloro-ethanone (0.650g, 95% yield).

Preparation of 4-(5-Bromo-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine



[0473] A solution 1-(5-Bromo-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-chloro-ethanone (0.56g, 1.97 mmol) and thio urea (0.16 g, 2.17 mmol) in ethanol (19mL) was stirred at 80 °C for 2 hours. The resulting precipitate was filtered, washed with MeOH, and dried under vacuum to give 4-(5-Bromo-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine (0.604g, 99% yield).

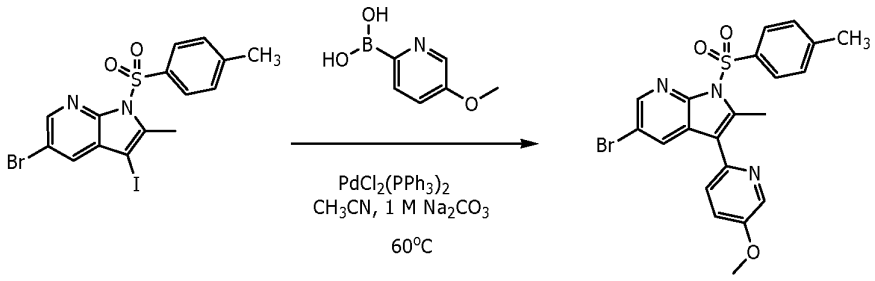
Preparation of 4-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-thiazol-2-ylamine (Example 267)



[0474] In a personal chemistry microwave reaction vial 4-(5-bromo-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-thiazol-2-ylamine (0. 2g, 0.64 mmol) and 1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine (0.23 g, 0.71 mmol), bis(triphenylphosphine)-palladium(II) dichloride (0.004 g, 0.006 mmol) in acetonitrile (2mL), and 1 M Na_2CO_3 (2 mL) were added. The resulting mixture was de-gassed with N_2 for 10 min, after which it was heated at 175°C for 30 min in a Personal Chemistry Optimizer. The mixture was diluted with DMF (3mL), and concentrated *in vacuo* and purified on silica gel column using dichloromethane and methanol to afford 4-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-thiazol-2-ylamine.

Example 279

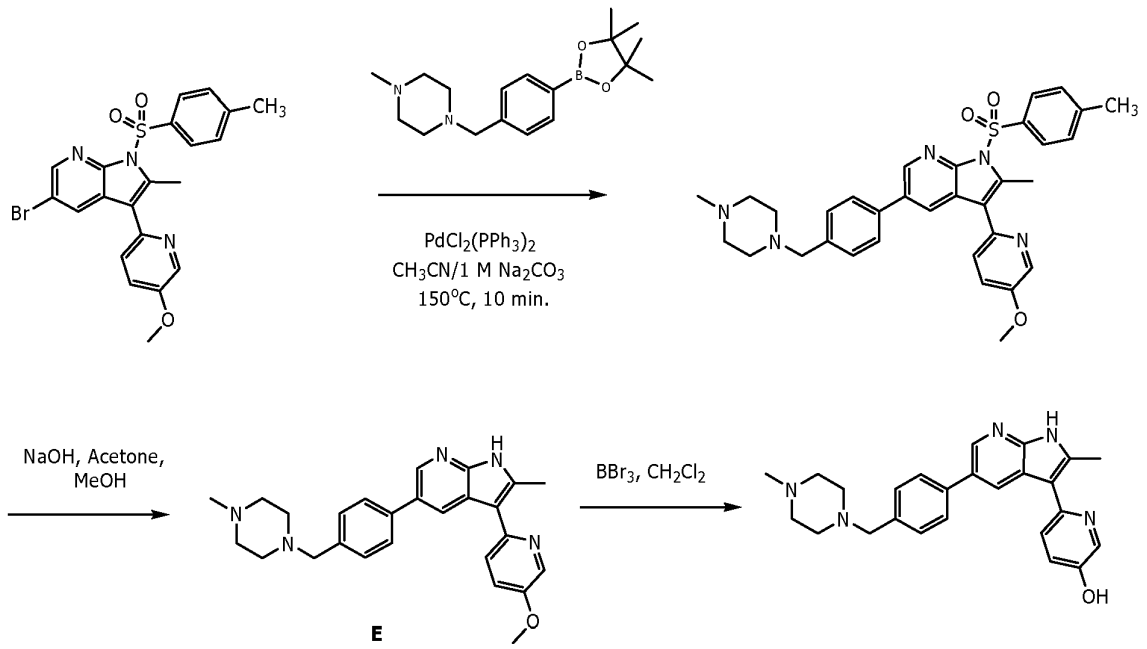
Preparation of 5-Bromo-3-(5-methoxy-pyridin-2-yl)-2-methyl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine



[0475] To a stirred suspension of 5-bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.25 g, 0.509 mmol) and 4-methoxy-2-pyridylboronic acid (0.094 g, 0.56 mmol) in DMF (1 mL) was added Cs_2CO_3 (0.663 g,0.05 mmol), dppf (0.028g, 0.05 mmol) followed by palladium acetate (0.011 g, 0.05 mmol). The resulting mixture was heated in personal microwave at 150°C for 1 hour. After consumption of the starting material, the mixture was evaporated to dryness *in vacuo*, absorbed onto Celite, and dried. The residue was purified via silica gel chromatography using CH_2Cl_2 as the eluent to obtain 5-bromo-3-(5-methoxy-pyridin-2-yl)-2-methyl-1-(toluene-

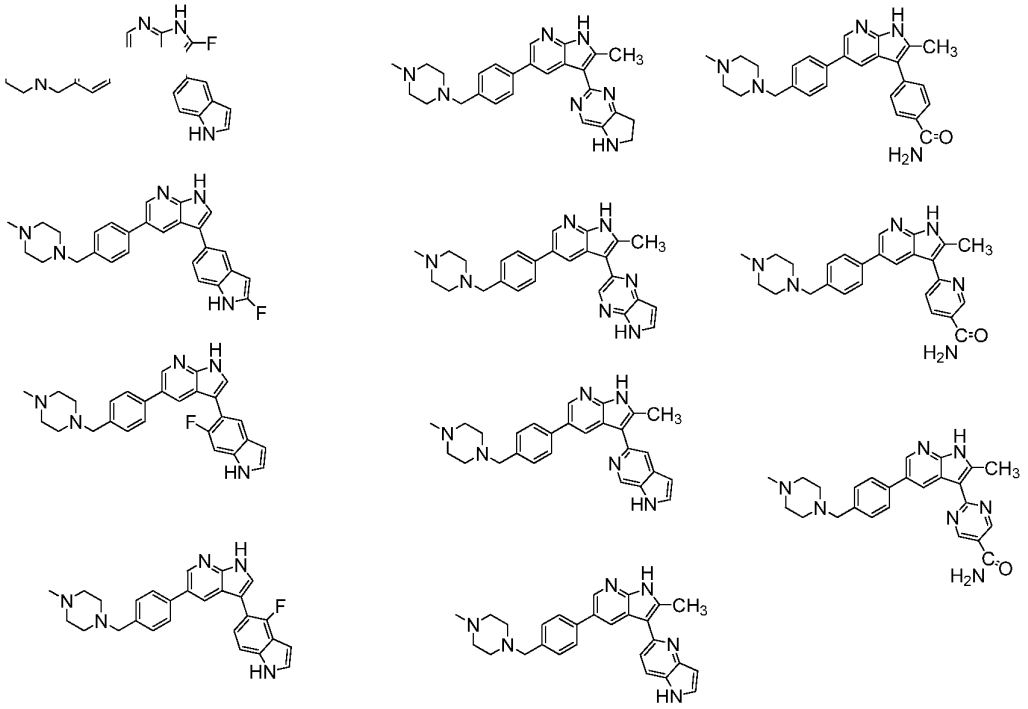
4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (0.120 g, 50%). MS ESI (m/z): 472/474 $(M+1)^+$, calc. 472.36.

Preparation of 6-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-pyridin-3-ol



To a solution of 5-bromo-3-(5-methoxy-pyridin-2-yl)-2-methyl-1-(toluene-4-sulfonyl)-1H-pyrrolo[2,3-b]pyridine (0.120g, 0.25 mmol) in CH_3CN (2.5 mL) in a Personal Chemistry microwave reaction vial was added 1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazine (0.161 g, 0.50 mmol), bis(triphenylphosphine)-palladium(II) dichloride (0.002 g, 0.002 mmol), and 1 M Na_2CO_3 (1 mL). The resulting mixture was de-gassed with Ar for 10 min, after which it was heated at 150°C for 30 min in a Personal Chemistry Optimizer. The organic layer was separated, filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL) and acetone (2 mL), and 2 M NaOH (1.5 mL) was added. The resulting mixture was stirred at 65°C for 30 min, after which it was partitioned between EtOAc and 1 M NaOH. The organic layer was separated, dried over $MgSO_4$, filtered, and stripped to give a residue purified on silicagel column to give brown solid. The solid was dissolved in CH_2Cl_2 (2.5 mL) and added 1M boron tiribromide solution in CH_2Cl_2 (1 mL). The resulting reaction mixture was stirred for 2 hours at room temperature and solvents evaporated and residue was purified on silica gel column to afford 6-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-pyridin-3-olas a white solid. MS ESI (m/z): 414 (M+1), calc. 413.51.

[0476] The following compounds can generally be made using the methods described above. It is expected that these compounds when made will have activity similar to those that have been made in the examples above.



Biological Activity

[0477] The activity of the compounds in Examples 1-207 as MLK and/or inhibitors is illustrated in the following assays. The other compounds listed above, which have not yet been made and/or tested, are predicted to have activity in these assays as well.

Radiometric filter plate MLK3 assay

[0478] 200ng (130nM) MLK3 (Dundee, DU8313) was incubated with 1μM inactive MKK7b (Dundee, DU703) in the presence of 2μM cold ATP (K_m) and 0.5μCi/assay ^{33}P ATP and appropriate concentrations of compounds. After a twenty minute incubation, the reactions were washed through filter plates and read on a scintillation counter. Results are shown in Table 10 below, in which +++ indicates ≤ 0.1 μM, ++ indicates >0.1 μM and ≤1 μM, and + indicates >1 μM.

Table 10.

Example	MK3 IC_{50}	MW
1	++	399.45
2	++	369.43
3	+++	366.5
4	+++	325.5
5	+++	354.5
6	++	340.39
7	+++	408.5
8	+++	324.5
9	+++	326.36
10	++	394.48
11	+++	402.5
12	++	348.41
13	++	353.43
14	++	309.13
15	+++	375.43
16	+++	417.47
17	+++	377.41
18	+++	376.42
19	+++	404.47
20	+	304.32
21	++	358.45
22	+	366.83
23	++	301.35
24	+++	413.48
25	+++	403.44
26	+++	373.14
27	++	358.14
28	++	329.13
29	+	338.77

Example	MK3 IC_{50}	MW
30	+++	339.15
31	++	422.54
32	+++	421.55
33	+++	366.47
34	+++	467.58
35	+	426.52
36	+++	400.44
37	+++	370.41
38	+++	355.4
39	+++	469.55
40	+++	417.43
41	++	431.16
42	+	357.12
43	+	369.16
44	+	328.11
45	++	343.11
46	+	355.14
47	++	387.13
48	+	395.03
49	+	375.11
50	++	372.13
51	++	371.4
52	++	412.45
53	++	366.39
54	++	343.35
55	+++	373.37
56	+	366.39
57	+++	486.53
58	++	379.33
59	+++	379.33

Example	MK3 IC_{50}	MW
60	+++	372.39
61	+	363.33
62	+++	403.4
63	++	385.39
64	+	385.43
65	+	387.4
66	+	426.5
67	++	485.55
68	++	408.42
69	+	378.39
70	+	334.34
71	+	319.33
72	+++	431.45
73	+	410.27
74	+++	370.41
75	+	340.39
76	++	296.33
77	+	281.32
78	++	356.38
79	++	326.36
80	+	335.2
81	+	282.3
82	+	267.29
83	++	418.42
84	++	357.37
85	+	342.36
86	+	351.41
87	+	388.39
88	+	329.32
89	+	413.44

Example	MK3 IC_{50}	MW
90	++	418.42
91	++	388.39
92	+	344.34
93	++	329.32
94	+	370.41
95	+	356.39
96	++	435.46
97	++	361.38
98	+	346.37
99	+	373.44
100	+	430.49
101	+	418.46
102	+++	418.42
103	++	388.39
104	++	413.44
105	++	378.39
106	++	348.36
107	++	425.49
108	++	439.52
109	+	464.48
110	+++	418.46
111	++	388.39
112	+++	418.42
113	+++	418.42
114	++	394.5
115	++	364.5
116	++	389.5
117	+	296.33
118	++	325.37
119	+	390.83

Example	MK3 IC_{50}	MW
120	++	328.37
121	++	354.41
122	+	413.4
123	++	354.41
124	++	416.44
125	+	355.4
126	+	401.43
127	+	372.45
128	++	389.4
129	+	389.4
130	+	388.42
131	++	431.44
132	+	431.44
133	+	413.43
134	+	413.43
135	+	391.42
136	+	391.42
137	+	390.44
138	+	433.46
139	++	480.55
140	+	449.55
141	+++	435.52
142	+++	421.49
143	+++	435.52
144	+++	507.63
145	++	435.52
146	+++	463.53
147	+++	435.52
148	+++	525.6
149	+++	425.48

Example	MK3 IC_{50}	MW
150	++	467.52
151	+++	525.6
152	++	HCl-salt: 461.94
153	++	467.52
154	++	419.43
155	++	425.53
156	+++	425.53
157	+++	453.54
158	+++	439.51
159	+++	431.48
160	++	507.58
161	++	521.61
162	+++	425.53
163	+	421.54
164	+	417.46
165	+++	439.55
166	++	378.4
167	++	426.47
168	++	507
169	+++	408
170	+	400
171	+	450
172	++	412
173	++	435
174	++	422
175	++	437
176	++	439
177	++	442
178	++	497

Example	MK3 IC_{50}	MW
179	+++	407
180	++	453
181	++	491
182	+++	505
183	+++	479
184	+++	465
185	++	493
186	+++	477
187	+++	463
188	+++	479
189	+++	499
190	+++	485
191	+++	479
192	+++	493
193	+++	489
194	+++	491
195	+++	518
196	++	489
197	+++	463
198	+++	436
199	+++	389
200	+++	449
201	++	449
202	+++	422
203	+++	433
204	NT	440
205	NT	436
206	+++	423
207	NT	476

DLK and LRRK Activity

[0479] Compounds were tested for activity by Ambit Biosciences (San Diego, CA) against the DLK and LRRK2 kinases as described in Karaman *et al.*, "A quantitative analysis of kinase inhibitor selectivity," *Nature Biotechnology*, 2008 January 26(1): 127-132. Certain compounds disclosed herein exhibited activity in the assay as against one or both of these targets.

[0480] Dominant mutations of LRRK2 are the most common cause of inherited Parkinson's Disease (PD), a debilitating, progressive neurodegenerative disorder characterized by motor and cognitive dysfunction which affects >1 million people in North America alone. Most cases of LRRK2-related PD are clinically and pathologically indistinguishable from the idiopathic disease. LRRK2 contains both GTPase and kinase domains, as well as two protein–protein interactions domains (leucine-rich and WD40 repeats). Definitively pathogenic mutations have been identified in the GTPase and kinase domains, as well as the region between these domains. Significant efforts have been made to determine whether PD mutations alter LRRK2 kinase activity. There is consensus that G2019S significantly increases LRRK2 kinase function in assay of either autophosphorylation or phosphorylation of generic substrates. LRRK2 mutations appear to cause a toxic gain of function that requires intact kinase function. Inhibition of LRRK 2 represents a therapeutic strategy for the treatment of PD.

DLK In Vitro Assay

[0481] In neuronal cells, DLK specifically activates MKK7 (S. E. Merritt *et al.*, J Biol Chem 274, 10195 (1999)). Inhibition potency of the new compounds against native DLK may be measured by using an in vitro kinase assay adapted from A. Daviau, M. Di Fruscio, R. Blouin, *Cell Signal* 21, 577 (2009).

[0482] DLK is immunoprecipitated from neuronally differentiated PC-12 cells (which are known to contain active DLK, see *e.g.*, Eto *et al.*, *Neurosci Res* 66, 37 (2010)). Compounds are then incubated with substrate (MKK7) plus radiolabelled ATP, in the presence or absence of selected compounds. NGF is added to PC12 cells to induce neurite outgrowth and differentiation into cells that resemble sympathetic neurons (50 ng/ml NGF will be added to cells for 6 days). The cells are lysed and DLK immunoprecipitated using specific antibodies and protein G agarose beads. DLK kinase activity is be assessed by an in vitro kinase assay using purified MKK7 (produced as a GST fusion protein in E. coli) as a specific enzyme substrate (8), in combination with radiolabelled ATP and the test compounds of interest (10, 100 nM; 1, 10 μM). DLK activity will be measured by performing SDS-PAGE and exposing the gel to a phosphorimager to quantitate the level of incorporated radioisotope. In parallel, MLK3 inhibition potency may also be analyzed, using an in vitro kinase assay with recombinant c-Jun as the substrate. Compounds

are expected to exhibit DLK/MLK inhibitory activity, including (i) DLK-specific, (ii) mixed DLK/MLK3-specific and (iii) MLK3-specific inhibitory activity.

DLK Cellular Assay

[0483] Compounds may also be analyzed for DLK inhibition potency using a cell-based assay. To do this, PC12 cells are neuronally differentiated with NGF, and then exposed to either hyperglycemic (25 mM) or euglycemic (5 mM) conditions, prior to treating cells with selected DLK/MLK inhibitors or vehicle. Cell lysates are then prepared, DLK immunoprecipitated, and kinase activity assessed using the *in vitro* kinase assay outlined above. Exogenous DLK inhibitors are not added to the in vitro kinase reaction since they are already present as a complex with the native, cell-derived DLK in the cell lysates.

[0484] Differentiated PC12 cells have been used to model diabetic neuropathy, by exposing them to hyperglycemic (25mM) conditions for 6 days (E. Lelkes, B. R. Unsworth, P. I. Lelkes, *Neurotox Res* **3**, 189 (2001); F. Zhang, S. C. Challapalli, P. J. Smith, *Neuropharmacology* **57**, 88 (2009)). Therefore, PC12 cells may be differentiated in the presence of 50 ng/ml NGF, and media supplemented with glucose to expose cells to euglycemic (5 mM) or hyperglycemic (25 mM) conditions, in the presence or absence of selected DLK/MLK inhibitors (for example, at any one or more of 0.1, 1, 10, 100, or 1000 μM) or vehicle. Mannitol (5 or 25 mM) is used as an osmotic control. The cells are lysed at selected time points following exposure to hyper/eu-glycemic conditions (for example, at 1, 4, and/or 24 hours), and DLK immunoprecipitated. *In vitro* kinase assays may then be performed as described above, with the slight modification that exogenous DLK inhibitors will not be added to the *in vitro* kinase reaction. In parallel, cytotoxicity of the test compounds may also be assessed using MTT and trypan blue assays. Compounds are expected to exhibit kinase-inhibitory activity using a cell-based assay for inhibition of DLK. Exposure of cells to hyperglycemic conditions is expected to lead to enhanced DLK activity.

[0485] Results from these in vitro kinase assays may be correlated with data from functional neuroprotection experiments and small animal studies.

DLK inhibitors and axon outgrowth in cultured adult sensory neurons

[0486] The adult sensory neuron culture accurately represents the neuronal cell types found in the dorsal root ganglia (DRG) of the peripheral nervous system. The process of culturing these neurons involves axotomizing the cell bodies and several studies have demonstrated that the phenotypic properties of these neurons mimic those observed in the DRG in vivo upon peripheral nerve damage (I. Gavazzi, R. D. Kumar, S. B. McMahon, J. Cohen, *Eur J Neurosci* 11, 3405 (1999)). The DRG neurons are comprised of a variety of neuronal sub-types that

includes nociceptive neurons (NGF and GDNF sensitive), mechanoreceptive neurons (NGF, BDNF and NT-4 sensitive) and proprioceptive neurons (NT-3 sensitive) (S. Averill, S. B. McMahon, D. O. Clary, L. F. Reichardt, J. V. Priestley, *Eur J Neurosci* 7, 1484 (1995)). This culture system can be maintained under defined conditions in the absence of serum for up to one week before neuronal cell death begins. Upon plating the neurons rapidly initiate axon outgrowth and accurate measures of axonal outgrowth can be determined during the first 2 days in culture. During the first 2-3 days in vitro no neuronal death takes place, making interpretation of axon outgrowth a straightforward endeavor.

[0487] Cultures of adult sensory neuronsare used. Cultured adult neurons are fully differentiated and exhibit the properties of adult neurons in vivo – unlike embryonic neurons. All cultures are grown under defined conditions in the presence of Bottenstein's N2 additives. This allows, during the first 2-3 days in culture, an accurate assessment of axon outgrowth without interference from non-neuronal cells. The range of growth factors to be applied includes NGF, NT-3 and GDNF, to ensure that all the main sub-populations of neurons within this heterogeneous population will produce axonal outgrowth. The doses of the growth factors are sub-optimal, ensuring a level of axonal outgrowth that can be accurately measured but that can either be enhanced or reduced by test drugs. In order to mimic Type 1 diabetes, neuron cultures include 25mM glucose.

[0488] First, a primary screen may be performed of the DLK inhibitors for ability to enhance axon outgrowth against sensory neurons derived from normal adult rats. The primary screen uses sensory neurons derived from normal adult rats, and assesses effectiveness in promoting axon outgrowth. This culture represents the neuronal cell types found in the DRG of the peripheral nervous system. The impact of novel DLK inhibitors on various indices of axon outgrowth proposed to be a relevant in vitro measures of axon growth and degeneration in vivo in diabetic neuropathy is examined. Assessment of levels or patterns of axon outgrowth is performed at 1 day before non-neuronal cells begin to interfere using confocal microscopy, digital images are collected of fixed cultures stained for neuron specific ß-tubulin III. The images are then analyzed using SigmaScan Pro software to quantitate % neurite growth, total axon outgrowth and cell diameter.

[0489] Next, compounds identified as hits from the primary screen may be tested in a secondary screen against neurons isolated from 2-3 month STZ-diabetic rats. The assay may serve two purposes: first, to screen for drugs that enhance axon outgrowth in STZ-diabetic cultures (for methods, see above), and second,to assess the ability to prevent high [glucose]-induced axon degeneration (E. Zherebitskaya, E. Akude, D. R. Smith, P. Fernyhough, *Diabetes*

58, 1356 (2009)). Previous work has shown that under high [glucose] the axons exhibit oxidative stress-induced appearance of aberrant axonal swelling. Such structures can be identified by staining for amino acid adducts of 4-HNE and for accumulated mitochondria. Therefore, drug hits are analyzed quantitatively for the ability to prevent the formation of axonal swellings containing 4-HNE staining and accumulated mitochondria.

[0490] Measures of axonal outgrowth (% process-bearing neurons, total neurite length and cell diameter) are assessed using a Zeiss LSM LSM510 confocal inverted microscope and SigmaScan Pro software. Each compound is tested at 4 concentrations (*e.g.* 1, 10, 100, 1000 μM) in a 96-well plate format. At least 4 images at x20 magnification are collected from the central section of each well using a digital camera (=35-40 neurons); cells from 4-8 replicate wells are counted to generate mean values. Previous studies demonstrate acceptable error levels, and permit 2-fold differences in total axonal outgrowth to be detected at a statistically significant level (P. Fernyhough, G. B. Willars, R. M. Lindsay, D. R. Tomlinson, *Brain Res* 607, 117 (1993); N. J. Gardiner *et al.*, *Mol Cell Neurosci* 28, 229 (2005)). Statistical analyses are performed at the 5% significance level using one-way ANOVA and Dunnett's post hoc test for percentage of process-bearing neurons and total axon outgrowth. The Mann Whitney U-test is performed for comparing values for axon radii and cell diameter. Compound-treated cells are expected to show increased axonal outgrowth.

In Vivo Efficacy Assays

[0491] Compounds disclosed herein may be tested in any number of well-known and publicly available animal models of efficacy for diseases in which MLK3 or DLK inhibition may play a therapeutic role. It is within the capacity of one skilled in the art to select and tailor such a model.

STZ-diabetic mouse model of degenerative neuropathy

[0492] STZ-induced pancreatic beta cell destruction is a widely used means of inducing type 1 diabetes in adult rodents that excludes the impairments of maturation that can impede interpretation in genetic models of type 1 diabetes. Mice are used as structural damage to primary sensory neurons and sensory loss develop within 4 weeks of onset of diabetes (K. K. Beiswenger, N. A. Calcutt, A. P. Mizisin, *Neurosci Lett* **442**, 267 (2008)). These features take longer (8-12 weeks) to develop in STZ-diabetic rats (N. A. Calcutt, *Methods Mol Med* **99**, 55 (2004)).

[0493] The primary end points of paw thermal responses and paw skin intra-epidermal fiber (IENF) density provide an integrated functional and structural evaluation of small fiber sensory neuropathy in diabetic mice. The STZ-diabetic mouse model develops paw thermal hypoalgesia

and reduced IENF density within 4 weeks of onset of diabetes and neuropathy is not due to STZ neurotoxicity per se. Focus is on sensory neuropathy as it is the most common feature of clinical diabetic neuropathy and because it most closely aligns with the in vitro screening assays that use adult DRG sensory neurons.

[0494] Efficacy against motor nerve conduction velocity (MNCV) slowing may be assessed as a secondary end point as this is currently the most widely studied index of therapeutic potential in preclinical and clinical studies of diabetic neuropathy. The assay allows detection of MNCV slowing within 4 weeks of onset of STZ-induced diabetes in mice (T. F. Ng *et al.*, *Diabetes* 47, 961 (1998)). Finally, corneal sensory nerve retraction may be measured as an exploratory end point. Corneal confocal microscopy is an emerging technique that allows non-invasive visualization of corneal sensory nerves and provides a sensitive detection system for sensory neuropathy in diabetic patients (C. Quattrini *et al.*, *Diabetes* 56, 2148 (2007)).

[0495] A prevention paradigm may be initially employed in which treatment begins within days of onset of diabetes. This approach offers the most likely chance of detecting a positive effect, a rapid screening time (4 weeks of diabetes) and is consistent with evidence that DLK activation promotes neurodegeneration (B. R. Miller *et al.*, *Nat Neurosci* 12, 387 (2009)).

[0496] Alternatively or in conjunction, a reversal paradigm may be employed in which treatment does not begin until after sensory neuropathy is established. The reversal paradigm takes longer and includes the risk that neurons already on a path towards degeneration and death are beyond the point of rescue. However, the potential to halt degeneration *and* promote regeneration would offer additional therapeutic use in patients with neuropathy.

[0497] The experimental model uses adult female C57Bl/6J mouse injected ip with 90 mg/kg STZ, i.p. for 2 consecutive days. Diabetes is confirmed by blood glucose of > 15 mmol/l on day 5 after STZ and at the end of the study; body weight is measured weekly. Exposure to test drugs is for 4 weeks (prevention) or 8 weeks (intervention: 4 weeks untreated and 4 weeks treated) using a dose, route and frequency determined based upon compound properties including efficacy and/or potency. Group size may be 12 animals (based on previous studies) and, for prevention studies, may include an evaluation of 3 different dose levels. Outcome measures are as follows:

[0498] Paw thermal response latency is measured by the Hargreaves method (K. K. Beiswenger, N. A. Calcutt, A. P. Mizisin, *Neurosci Lett* **442**, 267 (2008); N. A. Calcutt, *Methods Mol Med* **99**, 55 (2004)) at weeks 4 (prevention and intervention) and 8 (intervention). IENF density is measured in paw skin collected at autopsy (week 4 for prevention and weeks 4 and 8 for intervention). Skin is processed to paraffin blocks and sections stained with PGP9.5 prior to

counting of immunostained nerve fibers in the epidermis and calculation relative to length of the dermal:epidermal junction. Additional data collected may include epidermal thickness and frequency of Langerhans' cells and sub-epidermal nerves (see Bensweger *et al.*). Sciatic MNCV may be measured in the sciatic tibial nerve system under recovery isoflurane anesthesia using the M wave of evoked paw muscle EMG at weeks 0, 4 & 8 (intervention). Corneal confocal nerves may be visualized using an HRT II corneal confocal microscope with a Rostok Cornea Module, as used in studies of human and rodent corneal nerves. Mice are anesthetized with isoflurane and corneal nerve images collected for analysis of axon density, length and branching as described in human studies (see Quattrini *et al.*). Measurements may be made at weeks 0, 4 and 8 (intervention). All data are parametric and are analyzed by one-way ANOVA with between-group differences identified by the Student-Newman-Keuls or Dunnett's *post-hoc* tests as appropriate. Compounds tested are expected to demonstrate activity in the model, inclusing decreased paw thermal response, increased IENF density, reduced MNCV slowing, and other measures indicative of diabetic neuropathy.

Testing of compounds for efficacy in established HIV-1–encephalitic

(HIVE) mouse model

[0499] For example, compounds disclosed herein can be ranked for *in vivo* efficacy in a mouse model relevant to NeuroAids (D. Eggert, The Journal of Immunology, in press, November 2009.) Test compounds selected may be prioritized based on MLK3 potency and favorable exposure in the brain, but this is not an absolute requirement. Four-week-old male CB-17/IcrCrl-SCIDbr (CB17/SCID) mice may be purchased from Charles River Laboratory. HIV-1ADA–infected MDM (1.5×10^5 cells infected at an MOI of 0.1 in 5 ml) is stereotactically injected intracranially after 1 day of viral infection and referred to as HIVE mice. The test compound is then administered i.p. daily for 7 days at doses 0.5, 1.0, 1.5, 5.0, and 15.0 mg/kg/d (where, *e.g.*, n = 4 mice/treatment group). Vehicle only serves as the control. CB17/SCID mice receive intracranial (i.c.) injections of media (sham-operated) and serve as additional controls. Animals are treated with vehicle or test compound (*i.e.*, a compound as disclosed herein) starting 1 d post-i.c. injection and for 7 d after MDM injections and test compound treatments. Dosing parameters, number per group, etc. may be varied as needed, and such variations are within the skill of one skilled in the art.

Histopathology and image analysis

[0500] Brain tissue is collected at necropsy, fixed in 4% phosphate-buffered paraformaldehyde, and embedded in paraffin. Paraffin blocks are cut until the injection site of

the human MDM is identified. HIV-1 p24 Ag (cloneKal-1; Dako, Carpinteria, CA) is used to test for virus-infected human MDM. For each mouse, 30–100 serial (5-mm-thick) sections are cut from the injection site and three to seven sections (10 sections apart) analyzed. Abs to vimentin intermediate filaments (clone VIM 3B4; Boehringer Mannheim, Indianapolis, IN) are used for detection of human cells in mouse brains. Mouse microglia are detected by Abs to Iba-1 (WAKO, Osaka, Japan), and astrocytes are detected by Abs for glial fibrillaryacidic protein ([GFAP] Dako). NeuN, MAP-2 (both from Chemicon International), and H chain (200 kDa) neurofilaments (Dako) are used for detection of neurons. All sections are counterstained with Mayer's hematoxylin. The numbers of human MDM and HIV-1 p24 Ag-positive cells are counted with a Nikon Microphot-FXA microscope. All obtained images are imported into Image-Pro Plus, v. 4.0 (Media Cybernetics, Silver Spring, MD) for quantifying area (%) of GFAP, Iba-1, MAP-2, and NeuN positive staining. Efficacious MLK inhibitors will exhibit a dose-dependent reduction in microgliosis and restoration of normal synaptic architecture relative to control animals. Compounds disclosed herein can be tested according to this method and are expected to exhibit similar results.

Pharmacokinetic Studies

[0501] Compounds disclosed herein may be evaluated in pharmacokinetic assays and models to determine absorption, distribution, metabolism, and excretion parameters. The choice and tailoring of in vitro and ex vivo assays and in vivo models will vary according to the route of administration/formulation, indication under study, properties of test compounds, etc., as well as according to such factors as costs, availability of technology and res0urces, etc. Such parameters are well known in the fields of pharmacology and drug development. It is within the capacity of one skilled in the art to design and carry out, such work, or to outsource it to a capable third party.

Pharmacokinetic Evaluation in Mice

[0502] Several compounds disclosed herein were evaluated in a standard murine pharmacokinetic model. Compounds were selected that exhibited reasonable solubility and metabolic stability, and good predicted blood brain barrier penetration, based on low molecular weight, a low number of hydrogen bond donors, logD within a range of 2-4, and low polar surface area.

[0503] Compounds were dissolved in either 5% DMSO, 40% PEG400, and 55% saline (pH=8) or % DMSO, 40% PEG400, and 55% (20% HP-β-CD in deionized water; pH=8) to yield a nominal concentration of 2 mg/mL for intravenous administration. Compounds were administered via a single intravenous (IV) injection in CL57 BL/6 mice at 10 mg/kg in

DMSO/PEG400 solution. Three mice in each group were used for blood and brain collection at each time point. Blood samples (300 μL) were collected via the retro-orbital vein predose and at 5 min, 0.25, 0.50, 1, 2, 4, 6, 8, and 24 hours postdose. Blood samples were placed into tubes containing sodium heparin and centrifuged under refrigerated conditions at 8000 rpm for 6 minutes to separate plasma from the samples. The brain of each animal was collected after the final blood collection. The whole tissue was harvested, excised and rinsed by saline, dried by filter paper, and then placed into one tube per tissue per animal. All samples were stored at -20°C until bioanalysis.

[0504] Compound concentrations in plasma and brain homogenate were determined using a high performance liquid chromatography/mass spectrometry (HPLC/MS/MS) method (Agilent 1100 series HPLC, AB Inc. API4000 triple-quadrupole with an ESI interface and Analyst 1.4 software).

[0505] Results in the form of area under the time-versus-concentration curve (AUC) are given below in Table 11. Additional compounds disclosed herein can be tested according to this method and are expected to exhibit similar results.

Table 11.

Ex.	**AUC Plasma** + indicates ≥1500 - indicates <1500	**AUC Brain** + indicates ≥500 - indicates <500
1	+	+
4	-	-
9	+	+
17	+	-
18	+	-
32	+	+

[0506] This application incorporates by reference United States Provisional Applications No. 61/117,950, filed November 25, 2008, No. 61/148,755 filed January 30, 2009, and No. 61/148,778 filed January 30, 2009, and PCT Application No. PCT/US09/65878, filed November 25, 2009, as if written herein in their entireties.

[0507] It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be

suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. In addition, any elements or limitations of any invention or embodiment thereof disclosed herein can be combined with any and/or all other elements or limitations (individually or in any combination) or any other invention or embodiment thereof disclosed herein, and all such combinations are contemplated with the scope of the invention without limitation thereto.

[0508] It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

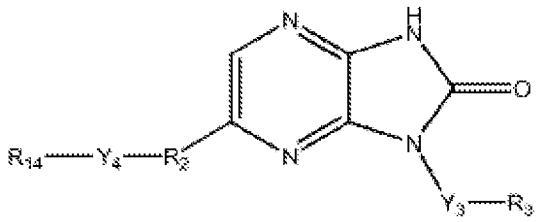
[0509] In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

2011258465 22 Nov 2016

CLAIMS

What is claimed is:

1. A compound of structural Formula VI



(VI)

or a salt thereof, wherein:

Y_3 is chosen from a bond, C_1-C_6 straight or branched chain alkyl, C_{1-6} straight or branched chain heteroalkyl and C(O)R", where R" is chosen from C_1-C_6 straight or branched chain alkyl, cycloalkyl, cycloheteroalkyl, and C_1-C_6 straight or branched chain heteroalkyl, any of which are optionally substituted with OH, (O), or halogen;

Y_4 is chosen from O, S, C(O), SO, SO_2, NH, $N(CH_3)$, CH_2, CHF, CF_2, $CH(CH_3)$, $C(CH_3)_2$, CH_2O—, and —CH_2N—; and

R_2 is chosen from phenyl and 6-membered monocyclic heteroaryl, either of which is optionally substituted with one or more substituents chosen from deuterium, halogen, hydroxy, C_1-C_6 amido, C_1-C_3 alkoxy, C_1-C_3 alkyl and NRR' where R and R' are independently chosen from H, unsubstituted C_1-C_6 straight or branched chain alkyl, and unsubstituted C_1-C_6 straight or branched chain heteroalkyl;

R_3 is chosen from cycloalkyl, aryl, heteroaryl, and bicyclic heteroaryl, any of which is optionally substituted with one or more substituents chosen from deuterium, halogen, hydroxy, C_1-C_6 amido, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), cyano, haloalkyl, phenyl, cycloalkyl, heteroaryl, cycloheteroalkyl, NRR' where R and R' are independently chosen from H, unsubstituted C_1-C_6 straight or branched chain alkyl and unsubstituted C_1-C_6 straight or branched chain heteroalkyl; and C(O)R", where R" is chosen from C_1-C_6 straight or branched chain alkyl, cycloalkyl, cycloheteroalkyl, and C_1-C_6 straight or branched chain heteroalkyl, any of which are optionally substituted with OH, (O), or halogen;

R_{14} is chosen from a 3 to 6 membered monocyclic heterocycloalkyl having between 1 and 4 heteroatoms chosen from O, S, and N, and five or six membered monocyclic heteroaryl having between 1 and 4 heteroatoms chosen from O, S, and N, and bicyclic heteroaryl where

each ring is a five or six membered ring, and where the bicyclic heteroaryl has between 1 and 4 heteroatoms chosen from O, S, and N, any of which is optionally substituted with one or more substituents chosen from deuterium, halogen, hydroxy, C_1-C_6 amido, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), haloalkyl, phenyl, benzyl, 3 to 6 membered monocyclic cycloalkyl, NRR' where R and R' are independently chosen from H, unsubstituted C_1-C_6 straight or branched chain alkyl and unsubstituted C_1-C_6 straight or branched chain heteroalkyl; and C(O)R", where R" is chosen from C_1-C_6 straight or branched chain alkyl, cycloalkyl, cycloheteroalkyl, and C_1-C_6 straight or branched chain heteroalkyl, any of which are optionally substituted with OH, (O), or halogen.

2. The compound of claim 1, wherein R_2 is phenyl optionally substituted with one or more substituents chosen from halogen, hydroxy, C_1-C_6 amido, C_1-C_3 alkoxy, C_1-C_3 alkyl and NRR' where R and R' are independently chosen from H, unsubstituted C_1-C_6 straight or branched chain alkyl and unsubstituted C_1-C_6 straight or branched chain heteroalkyl.

3. The compound of claim 1 or 2, wherein Y_4 is O, S, C(O), NH, or CH_2.

4. The compound of any one of claims 1 to 3, wherein R_{14} is a monocyclic heterocycloalkyl optionally substituted with one or more substituents chosen from halogen, hydroxy, C_1-C_6 amido, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), haloalkyl, phenyl, benzyl, 3 to 6 membered monocyclic cycloalkyl, NRR' where R and R' are independently chosen from H, unsubstituted C_1-C_6 straight or branched chain alkyl and unsubstituted C_1-C_6 straight or branched chain heteroalkyl; and C(O)R", where R" is chosen from C_1-C_6 straight or branched chain alkyl, cycloalkyl, cycloheteroalkyl, and C_1-C_6 straight or branched chain heteroalkyl, any of which are optionally substituted with OH, (O), or halogen.

5. The compound of any one of claims 1 to 3, wherein R_{14} is piperazinyl or morphilino, optionally substituted with one or more substituents chosen from halogen, hydroxy, C_1-C_6 amido, C_1-C_3 alkoxy, C_1-C_3 alkyl, (O), (S), haloalkyl, phenyl, benzyl, 3 to 6 membered monocyclic cycloalkyl, NRR' where R and R' are independently chosen from H, unsubstituted C_1-C_6 straight or branched chain alkyl and unsubstituted C_1-C_6 straight or branched chain heteroalkyl; and C(O)R", where R" is chosen from C_1-C_6 straight or branched chain alkyl, cycloalkyl, cycloheteroalkyl, and C_1-C_6 straight or branched chain heteroalkyl, any of which are optionally substituted with OH, (O), or halogen.

6. The compound of any one of claims 1 to 5, wherein R_2 is substituted with 0 to 3 substituents R_{15}, which each R_{15} is independently chosen from fluorine, hydroxy, NH_2, $NH(CH_3)$, $N(CH_3)_2$, methoxy, and methyl.

7. The compound of any one of claims 1 to 6, wherein Y_3 is a bond or CH_2.

8. The compound of any one of claims 1 to 7, wherein R_3 is phenyl or 5/6-fused bicyclic heteroaryl, either of which is optionally substituted with one or more substituents chosen from halogen, hydroxy, cyano, C_1-C_6amido, phenylamido, phenylalkylamido, 3 to 6 membered monocyclic heterocycloalkyl having between 1 and 4 heteroatoms chosen from O, S, and N, five or six membered monocyclic heteroaryl having between 1 and 4 heteroatoms chosen from O, S, and N, bicyclic heteroaryl where each ring is a five or six membered ring, and where the bicyclic heteroaryl has between 1 and 4 heteroatoms chosen from O, S, and N, C_1-C_6 alkyl heterocycloalkyl, C_1-C_3 alkoxy, C_1-C_3 alkyl and NRR' where R and R' are independently chosen from H, unsubstituted C_1-C_6 straight or branched chain alkyl, and unsubstituted C_1-C_6 straight or branched chain heteroalkyl.

9. The compound of any one of claims 1 to 7, wherein R_3 is chosen from benzothiazolyl, pyrrolopyridinyl, indanyl, cyclopropyl, cyclopentyl, phenyl, pyridinyl, pyrimidinyl, and indolyl, any of which is optionally substituted with one or more substituents chosen from fluorine, chlorine, hydroxy, NH_2, $NH(CH_3)$, $N(CH_3)_2$, $C(O)NH_2$, $C(O)NHCH_3$, morpholino, piperazinyl, methylpiperazinyl, acetamido, methylacetamido, methylpropionamido, phenylacetamidomethylene, benzamidomethylene, phenylpropanamidomethylene, methoxy, and methyl.

10. The compound of any one of claims 1 to 7, wherein R_3 is phenyl optionally substituted with one or more substituents chosen from hydroxyl, C_1-C_6 straight or branched chain alkyl, C_1-C_6 straight or branched chain alkoxy, C_1-C_6 straight or branched chain haloalkyl, C_1-C_6 straight or branched chain haloalkoxy, halogen, cyano, NRR' where R and R' are independently chosen from H, unsubstituted C_1-C_6 straight or branched chain alkyl and unsubstituted C_1-C_6 straight or branched chain heteroalkyl; and C(O)R", where R" is chosen from C_1-C_6 straight or branched chain alkyl, cycloalkyl, cycloheteroalkyl, and C_1-C_6 straight or branched chain heteroalkyl, any of which are optionally substituted with OH, (O), or halogen.

11. The compound of any one of claims 1 to 10, wherein R_2, R_3, or R_{14} is substituted with deuterium, fluorine, or methyl.

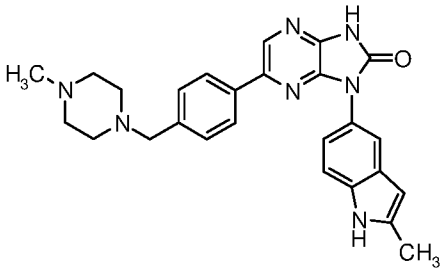
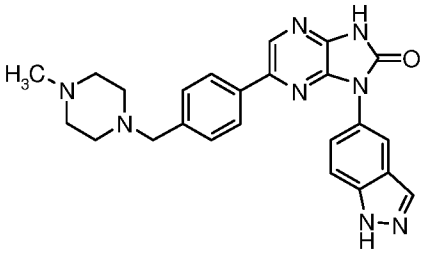
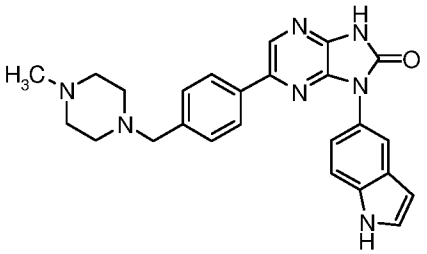
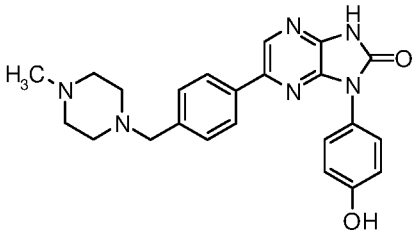
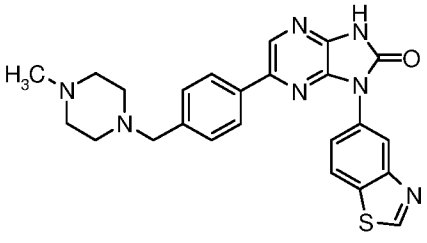
12. The compound of any one of claims 1 to 7, wherein R_3 is chosen from indanyl, indolyl, indazolyl, indolinonyl, benzothiophenyl, quinolinyl, isoquinolinyl, pyrrolopyrazinyl, and pyrrolopyridinyl, any of which is optionally substituted with one or more substituents chosen from hydroxy, C_1-C_6 straight or branched chain alkyl, C_1-C_6 straight or branched chain alkoxy, C_1-C_6 straight or branched chain haloalkyl, C_1-C_6 straight or branched chain haloalkoxy, halogen, NRR' where R and R' are independently chosen from H, unsubstituted C_1-C_6 straight or branched chain alkyl and unsubstituted C_1-C_6 straight or branched chain heteroalkyl; and C(O)R", where R" is chosen from C_1-C_6 straight or branched chain alkyl, cycloalkyl, cycloheteroalkyl, and C_1-C_6 straight or branched chain heteroalkyl, any of which are optionally substituted with OH, (O), or halogen.

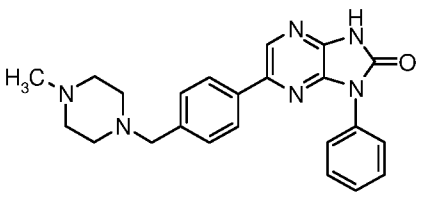
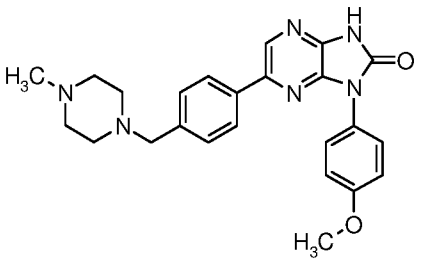
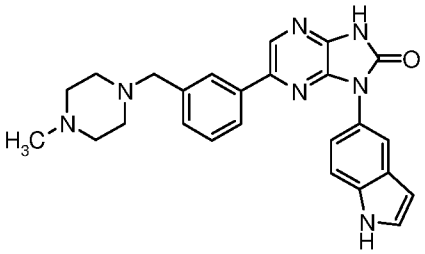
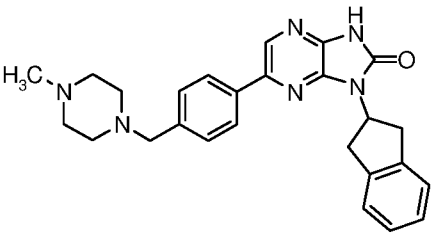
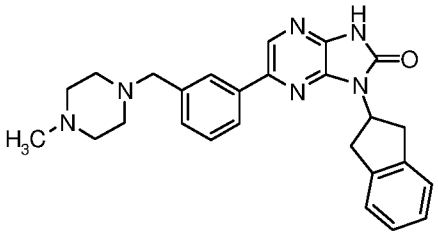
13. The compound of any one of claims 1 to 7, wherein R_3 is indanyl optionally substituted at a carbon atom with one or more substituents chosen from deuterium, halogen, and C_1-C_6 straight or branched chain alkyl.

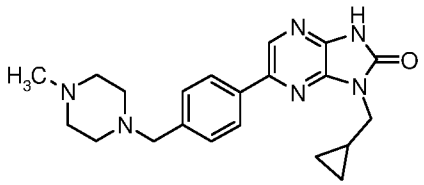
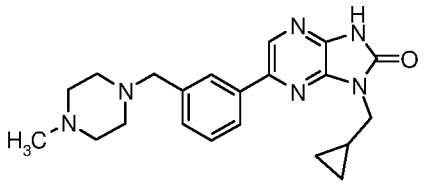
14. The compound of any one of claims 1 to 7, wherein R_3 is indanyl or phenyl optionally substituted with one or more substituents chosen from hydroxy, C_1-C_6 straight or branched chain alkyl, C_1-C_6 straight or branched chain alkoxy, C_1-C_6 straight or branched chain haloalkyl, C_1-C_6 straight or branched chain haloalkoxy, halogen, NRR' where R and R' are independently chosen from H, unsubstituted C_1-C_6 straight or branched chain alkyl and unsubstituted C_1-C_6 straight or branched chain heteroalkyl; and C(O)R", where R" is chosen from C_1-C_6 straight or branched chain alkyl, cycloalkyl, cycloheteroalkyl, and C_1-C_6 straight or branched chain heteroalkyl, any of which are optionally substituted with OH, (O), or halogen.

15. The compound of claim 1, wherein the compound is chosen from

Compound no.	Structure

224	
225	
226	
227	
228	

229	
230	
231	
235	
236	

237	
and 238	

16. A pharmaceutical composition comprising a compound of any one of claims 1 to 5 together with a pharmaceutically acceptable carrier.

17. A method of inhibition of MLK comprising contacting MLK with a compound of any one of claims 1 to 15.

18. The method of claim 17, wherein said MLK is MLK3.

19. The method of claim 17, wherein said inhibition is selective over other kinases.

20. A method of treatment of a MLK-mediated disease comprising the administration of a therapeutically effective amount of a compound of any one of claims 1 to 15 to a patient in need thereof.

21. The method of claim 20, wherein said disease is an inflammatory disease or a metabolic disease.

22. The method of claim 20 or 21, wherein said disease is chosen from diabetes mellitus, hyperglycemia, retinopathy, nephropathy, neuropathy, ulcers, micro- and macroangiopathies, gout and diabetic foot disease, insulin resistance, metabolic syndrome, hyperinsulinemia,

hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, and peripheral inflammation.

23. The method of claim 20, wherein said disease is an autoimmune disease.

24. The method of claim 20, wherein said disease is chosen from cancer and hepatitis.

25. A method of treatment of a MLK-mediated disease comprising the administration of:
a therapeutically effective amount of a compound of any one of claims 1 to 15; and
another therapeutic agent.

26. A MLK inhibitor comprising the compound of any one of claims 1 to 15.