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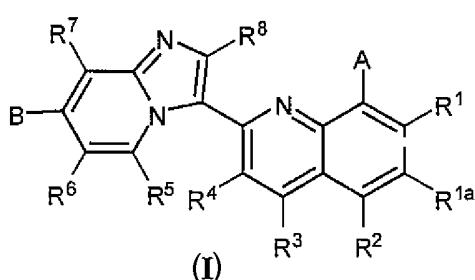
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(54) Title: IMIDAZO[1,2-A]PYRIDINE COMPOUNDS AS RECEPTOR TYROSINE KINASE INHIBITORS



(57) Abstract: Compounds of Formula I: in which A, B, R¹, R^{1a}, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ have the meanings given in the specification, are receptor tyrosine inhibitors useful in the treatment of diseases mediated by class 3 and class 5 receptor tyrosine kinases. Particular compounds of this invention have also been found to be inhibitors of Pim-1.

IMIDAZO[1,2-a]PYRIDINE COMPOUNDS AS RECEPTOR TYROSINE KINASE
INHIBITORS

[0001] The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to a process for making the compounds and to the use of the compounds in therapy. More particularly, it relates to certain imidazopyridine compounds useful in the treatment and prevention of diseases mediated by class 3 and class 5 receptor tyrosine kinases. Particular compounds of this invention have also been found to be inhibitors of Pim-1.

[0002] Receptor tyrosine kinases (RTK's) include the class 3 receptor tyrosine kinases (PDGF- α , PDGFR- β , MCSF-1R, c-kit, and FLT3) and the class 5 receptor tyrosine kinases (VEGFR and KDR). It is known that such kinases are frequently aberrantly expressed in common human cancers, such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer, renal cell carcinoma and gliomas.

[0003] FLT3 (fms-like tyrosine kinase; also known as Flk-2) is a member of the class 3 receptor tyrosine kinase (RTK) family, and is presumed to be involved in the hematopoietic system (Rosnet, et al., 1991, Genomics 9:380-385, Rosnet, et al., 1993, Blood 82:1110-1119). Aberrant expression of the FLT3 gene has been documented in both adult and childhood leukemias including acute myeloid leukemia (AML), AML with trilineage myelodysplasia (AML/TMDS), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS). Activating mutations of the FLT3 receptor have been found in about 35% of patients with acute myeloblastic leukemia (AML), and are associated with a poor prognosis. These types of mutations are associated with constitutive activation of the tyrosine kinase activity of FLT3, and result in proliferation and viability signals in the absence of ligand. Patients expressing the mutant form of the receptor have been shown to have a decreased chance for cure. In addition to activating mutations, ligand dependent (autocrine or paracrine) stimulation of over-expressed wild-type FLT3 contributes to AML. Thus, there is accumulating evidence for a role for hyper-activated (mutated) FLT3 kinase activity in human leukemias and myelodysplastic syndrome. FLT3 inhibitors may also be useful for treating immune related disorders and is involved in the process of angiogenesis through its expression in pericytes.

[0004] PDGFR is expressed on early stem cells, mast cells, myeloid cells, mesenchymal cells, and smooth muscles cells. PDGFR- β has been implicated in myeloid leukemias. Recently, it

was shown that activating mutations in PDGFR- α kinase domain are in gastrointestinal stromal tumors (GIST) (Wong et al., 2007, *Histopathology* 51(6): 758-762).

[0005] In addition, blockade of PDGF signaling has been shown to reduce the development of fibrosis in various experimental models (Yoshiji et al., 2006, *International Journal Molecular Medicine* 17: 899-904).

[0006] Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as inhibitors of the growth of mammalian cancer cells or for treating immune related disorders.

[0007] The Pim kinases are a family of three distinct vertebrate protein serine/threonine kinases (Pim-1, -2 and -3) belonging to the calmodulin-dependent protein kinase-related (CAMK) group. The over-expression of Pim-1 has been reported in various human lymphomas and acute leukemias (Amson, R. et al, *Proc. Natl. Acad. Sci. U.S.A.*, 1989, 86: 8857-8861). In addition, there is evidence that Pim-1 is over-expressed in prostatic neoplasia and human prostate cancer (Valdman, A. et al, *The Prostate*, 2004, 60: 367-371; Cibull, T.L. et al, *J. Clin. Pathol.*, 2006, 59: 285-288) and may serve as a useful biomarker in identification of prostate cancer (Dhanasekaran, S.M. et al, *Nature*, 2001, 412(13): 822-826). Recently, it has been discovered that Pim-1 is up-regulated by Flt-3 and may play an ancillary role in Flt-3 mediated cell survival (Kim, K.T. et al *Neoplasia*, 2005, 105(4): 1759-1767). Since Flt-3 itself is implicated in leukemias like AML, additional knockdown of Pim-1 may be a useful approach to treating leukemias driven by Flt-3 or various mutations. Accordingly, Pim-1 inhibitors may be useful as therapeutic agents for a variety of cancers such as hematological cancers.

[0008] Tyrosine kinase inhibitors are known in the art. U.S. Patent No. 7,125,888 describes certain imidazo[1,2-a]pyridine compounds substituted at the 3 position with a pyridyl, thiazolyl, oxazolyl or phenyl group and at the 7 position with an optionally substituted phenyl or pyridone group, which are purported to be tyrosine kinase inhibitors. U.S. patent publication 2005/0124637 discloses certain purine derivatives as inhibitors of receptor tyrosine kinases, including FLT3. PCT publication number WO 01/40217 and U.S. Patent No. 7,019,147 disclose certain benzimidazole compounds having activity as tyrosine kinase inhibitors.

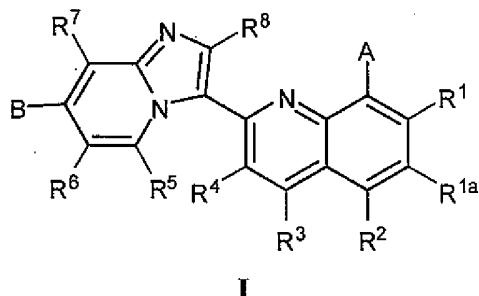
[0009] It has now been found that certain imidazo[1,2-a]pyridine compounds bearing a quinolinyl group at the 3 position of the imidazopyridine ring are inhibitors of receptor tyrosine kinases, in particular class 3 and class 5 receptor tyrosine kinases, which are useful for treating

diseases mediated by class 3 and class 5 receptor tyrosine kinases, such as cancers, fibrosis, sclerosis, autoimmune disorders and scleroderma.

[0010] In certain embodiments, the imidazopyridine compounds are class 3 receptor tyrosine kinases inhibitors. In particular embodiments, the compounds are inhibitors of the class 3 receptor tyrosine kinases PDGFR and FLT3.

[0011] A subset of compounds of the imidazopyridine compounds disclosed herein are also inhibitors of the kinase PIM-1.

[0012] Accordingly, provided is a compound of general Formula I:



[0013] or a pharmaceutically acceptable salt thereof, wherein:

[0014] A is -Z-(CH₂)_p-(hetCyc^{2a}), -Z-(hetCyc^{2b}), Z-R¹⁰ or Z-R¹¹;

[0015] Z is O or NH;

[0016] p is 0, 1, or 2;

[0017] hetCyc^{2a} is a 5 or 6 membered heterocyclic ring optionally substituted with one or more R⁹ groups;

[0018] hetCyc^{2b} is a 7-12 membered spirocyclic or bridged heterobicyclic ring system optionally substituted with one or more R⁹ groups;

[0019] R¹⁰ is (1-6C)alkyl substituted with NR'R";

[0020] R¹¹ is (5-6C)cycloalkyl substituted with NR'R";

[0021] B is H, CN, OR^h, Ar¹, hetAr², C(O)NRⁱR^j, C(O)-hetCyc³, C(O)NH(1-6C alkyl)-hetCyc³, C(O)(1-6C alkyl)-hetCyc³, SR^k, SO₂N(1-6C alkyl)₂, (1-6C alkyl)NR^lR^m or (1-3C)alkyl;

[0022] R¹, R^{1a}, R², R³ and R⁴ are independently H, F, Cl, CN, Me, Et, isopropyl, cyclopropyl, C(O)NRⁿR^o, CH₂OH, or hetAr³;

[0023] R⁵, R⁶, R⁷ and R⁸ are independently H, F, Cl, CN or Me;

[0024] each R⁹ is independently selected from halogen, CN, CF₃, (1-6C)alkyl, NR^aR^b, -(1-6C alkyl)NR^aR^c, OR^a, (1-6C alkyl)OR^a [optionally substituted with amino], C(O)NR^aR^c,

C(O)(CR^xR^y)NR^aR^c, NHC(O)R^e, NHC(O)(CR^mRⁿ)NR^aR^c, NHC(O)NR^fR^g, (1-6C alkyl)-hetAr¹, (1-6C alkyl)-hetCyc¹, oxo, and C(O)₂(1-6C alkyl);

[0025] each R^a is independently H or (1-6C)alkyl;

[0026] each R^b is independently H, (1-6C)alkyl, (1-6C alkyl)OH, (3-6C)cycloalkyl, CH₂hetAr⁴, (1-6C fluoroalkyl) or -(1-6C alkyl)-O-(1-6C alkyl),

[0027] each R^c is independently H, (1-6C)alkyl, (3-6C)cycloalkyl, or aryl;

[0028] each R^e is independently (1-6C alkyl);

[0029] each R^f and R^g is independently H or (1-6C alkyl);

[0030] R^h is H, CF₃, (1-6C)alkyl, (1-6Calkyl)-(3-6C cycloalkyl), (1-6C alkyl)-O-(1-6C alkyl), (1-6C alkyl)OH, (1-6C alkyl)-S-(1-6C alkyl), (1-6C alkyl)NR'R'', hetCyc⁴, (1-6C alkyl)hetCyc⁴, (1-6C alkyl)aryl, or (1-6C alkyl)-hetAr⁵;

[0031] Rⁱ is H or 1-6C alkyl;

[0032] R^j is (1-6C)alkyl, (1-6C alkyl)-O-(1-6C alkyl), or (1-6C alkyl)-OH;

[0033] R^k is (1-6C)alkyl, (3-6C)cycloalkyl, or (1-6C alkyl)-O-(1-6C alkyl);

[0034] R^m and Rⁿ are independently H or (1-6C alkyl);

[0035] R^x and R^y are independently H or (1-6C alkyl),

[0036] or R^x and R^y together with the atom to which they are attached form a cyclopropyl ring;

[0037] Ar¹ is aryl optionally substituted with OH, O-(1-6C alkyl), C(O)₂(1-6C alkyl), or (1-6C alkyl)NR'R'';

[0038] hetCyc¹ is a 5-6 membered heterocyclic ring which is optionally substituted with (1-6C)alkyl or OH;

[0039] hetCyc³ and hetCyc⁴ are independently a 5 or 6 membered heterocyclic ring optionally substituted with OH or -O(1-6C alkyl);

[0040] hetAr¹ and hetAr² are a 5-6 membered heteroaryl ring optionally substituted with one to three groups independently selected from (1-6C)alkyl, (3-6C)cycloalkyl, halogen, CN, CF₃, OCH₂F, OCF₃, O(1-6C alkyl), O(3-6C)cycloalkyl, and NR'R'';

[0041] hetAr³ and hetAr⁴ are independently a 5-6 membered heteroaryl ring ;

[0042] hetAr⁵ is a 5-6 membered heteroaryl ring optionally substituted with (1-6C)alkyl; and

[0043] R' and R'' are independently H or (1-6C)alkyl.

[0044] Compounds of Formula I include compounds wherein:

[0045] A is -Z-(CH₂)_p-(hetCyc^{2a}), -Z-(hetCyc^{2b}), Z-R¹⁰ or Z-R¹¹;

[0046] Z is O or NH;

[0047] p is 0, 1, or 2;

[0048] hetCyc^{2a} is a 5 or 6 membered heterocyclic ring optionally substituted with one or more R⁹ groups;

[0049] hetCyc^{2b} is a 7-12 membered spirocyclic or bridged heterobicyclic ring system optionally substituted with one or more R⁹ groups;

[0050] R¹⁰ is (1-6C)alkyl substituted with NR'R";

[0051] R¹¹ is (5-6C)cycloalkyl substituted with NR'R";

[0052] B is H, CN, OR^h, Ar¹, hetAr², C(O)NRⁱR^j, C(O)-hetCyc³, C(O)(1-6C alkyl)-hetCyc³, SR^k, SO₂N(1-6C alkyl)₂, or (1-6C alkyl)NR'R";

[0053] R¹, R^{1a}, R², R³ and R⁴ are independently H, F, Cl, CN, Me, Et, isopropyl, cyclopropyl, C(O)NR'R", CH₂OH, or hetAr³;

[0054] R⁵, R⁶ and R⁷ are independently H, F, Cl, CN or Me;

[0055] each R⁹ is independently selected from halogen, CN, CF₃, (1-6C)alkyl, NR^aR^b, -(1-6C alkyl)NR^aR^c, OR^a, (1-6C alkyl)OR^a [optionally substituted with amino], C(O)NR^aR^c, C(O)(CR^xR^y)NR^aR^c, NHC(O)R^e, NHC(O)(CR^mRⁿ)NR^aR^c, NHC(O)NR^fR^g, (1-6C alkyl)-hetAr¹, (1-6C alkyl)-hetCyc¹, oxo, and C(O)O(1-6C alkyl);

[0056] R^h is H, CF₃, (1-6C)alkyl, (1-6Calkyl)-(3-6C cycloalkyl), (1-6C alkyl)-O-(1-6C alkyl), (1-6C alkyl)OH, (1-6C alkyl)-S-(1-6C alkyl), (1-6C alkyl)NR'R", hetCyc⁴, (1-6C alkyl)hetCyc⁴, (1-6C alkyl)aryl, or (1-6C alkyl)-hetAr⁵;

[0057] Rⁱ is H or 1-6C alkyl;

[0058] R^j is (1-6C)alkyl, (1-6C alkyl)-O-(1-6C alkyl), or (1-6C alkyl)-OH;

[0059] R^k is (1-6C)alkyl, (3-6C)cycloalkyl, or (1-6C alkyl)-O-(1-6C alkyl);

[0060] Ar¹ is aryl optionally substituted with OH, O-(1-6C alkyl), C(O)₂(1-6C alkyl), or (1-6C alkyl)NR'R";

[0061] hetCyc³ and hetCyc⁴ are independently a 5 or 6 membered heterocyclic ring optionally substituted with OH;

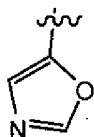
[0062] hetAr² is a 5-6 membered heteroaryl ring optionally substituted with one to three groups independently selected from (1-6C)alkyl, (3-6C)cycloalkyl, halogen, CN, CF₃, OCH₂F, OCF₃, O(1-6C alkyl), O(3-6C)cycloalkyl, and NR'R";

[0063] hetAr³ is a 5-6 membered heteroaryl ring;

[0064] hetAr⁵ is a 5-6 membered heteroaryl ring optionally substituted with (1-6C)alkyl; and

[0065] R' and R" are independently H or (1-6C)alkyl.

- [0066] In certain embodiments of Formula I, R¹ is H, F, Cl, Me, Et or isopropyl.
- [0067] In certain embodiments of Formula I, R¹ is H, F or Cl.
- [0068] In certain embodiments of Formula I, R¹ is H, Me, Et or isopropyl.
- [0069] In one embodiment, R¹ is H.
- [0070] In certain embodiments, R^{1a} is H, F, Cl, CN, Me, Et, or isopropyl.
- [0071] In certain embodiments, R^{1a} is H, F, Cl, or Me.
- [0072] In certain embodiments of Formula I, R^{1a} is H or F.
- [0073] In one embodiment, R^{1a} is H.
- [0074] In one embodiment, R^{1a} is F.
- [0075] In certain embodiments of Formula I, R² is H, F, Cl, Me, Et or isopropyl.
- [0076] In certain embodiments of Formula I, R² is H, F or Cl.
- [0077] In certain embodiments of Formula I, R² is H, Me, Et or isopropyl.
- [0078] In one embodiment, R² is H.
- [0079] In one embodiment, R² is F.
- [0080] In certain embodiments of Formula I, R³ is H, methyl, ethyl, isopropyl, cyclopropyl, or hetAr³. Examples of hetAr³ include 5 membered heteroaryl rings having a nitrogen atom and optionally having a second heteroatom selected from N and O. An example is oxazolyl. A particular value for R³ is the structure:



- [0081] In certain embodiments of Formula I, R³ is H, methyl, ethyl, isopropyl, or oxazolyl.
- [0082] In certain embodiments of Formula I, R³ is H, methyl, ethyl, or isopropyl.
- [0083] In certain embodiments of Formula I, R³ is H, methyl, or hetAr³.
- [0084] In certain embodiments of Formula I, R³ is H, methyl, or oxazolyl.
- [0085] In certain embodiments of Formula I, R³ is H.
- [0086] In certain embodiments of Formula I, R⁴ is H, F, Cl, Me, Et or isopropyl.
- [0087] In certain embodiments of Formula I, R⁴ is H, F or Cl.
- [0088] In certain embodiments of Formula I, R⁴ is H, Me, Et or isopropyl.
- [0089] In one embodiment, R⁴ is H.
- [0090] In one embodiment, R⁴ is F.

- [0091] In certain embodiments, R⁵, R⁶, R⁷ and R⁸ are independently selected from H, F and Me.
- [0092] In one embodiment, R⁵ is H.
- [0093] In one embodiment, R⁶ is H.
- [0094] In one embodiment, R⁷ is H.
- [0095] In one embodiment, R⁸ is H.
- [0096] In certain embodiments, of Formula I, each of R¹ and R⁴ is hydrogen.
- [0097] In certain embodiments, of Formula I, each of R⁵, R⁶, R⁷ and R⁸ is hydrogen.
- [0098] In certain embodiments, of Formula I, each of R¹, R⁴, R⁵, R⁶, R⁷ and R⁸ is hydrogen.
- [0099] In certain embodiments, of Formula I, each of R¹, R^{1a}, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ is hydrogen.
- [00100] In certain embodiments, A is -Z(CH₂)_p(hetCyc^{2a}).
- [00101] In certain embodiments, A is represented by the formula -NH-hetCyc^{2a}.
- [00102] In certain embodiments, A is represented by the formula -NH-(CH₂)-hetCyc^{2a}.
- [00103] In certain embodiments, A is represented by the formula -NH-(CH₂)₂-hetCyc^{2a}.
- [00104] In certain embodiments, A is represented by the formula -O-hetCyc^{2a}.
- [00105] In certain embodiments, A is represented by the formula -O-(CH₂)-hetCyc^{2a}.
- [00106] In certain embodiments, A is represented by the formula -O-(CH₂)₂-hetCyc^{2a}.
- [00107] Examples of hetCyc^{2a} include 5-6 membered heterocyclic rings having one or two heteroatoms independently selected from N and O. Particular values of hetCyc^{2a} include pyrrolidinyl, piperidinyl rings and morpholinyl rings. In certain embodiments, hetCyc^{2a} is substituted with one or more R⁹ groups. In certain embodiments, hetCyc^{2a} is unsubstituted:
- [00108] In certain embodiments, A is Z-hetCyc^{2b}.
- [00109] In certain embodiments, A is -NH(hetCyc^{2b}).
- [00110] In other embodiments, A is -O-(hetCyc^{2b}).
- [00111] Examples of hetCyc^{2b} include 7-11 membered bridged aza- or diaza-heterocycles. Particular values of hetCyc^{2b} include azabicyclo[2.2.1]heptane, azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.1]octane, diazabicyclo[2.2.1]heptane, and diazabicyclo[3.2.1]octane.
- [00112] In certain embodiments, hetCyc^{2b} is substituted with one or more R⁹ groups.
- [00113] In certain embodiments, hetCyc^{2b} is unsubstituted.

[00114] In certain embodiments, hetCyc^{2a} and hetCyc^{2b} are optionally substituted with one or more R⁹ groups independently selected from halogen, (1-6C)alkyl, NR^aR^b, -(1-6C alkyl)NR^aR^c, OR^a, (1-6C alkyl)OR^a [optionally substituted with amino], C(O)NR^aR^c, C(O)(CR^xR^y)NR^aR^c, NHC(O)R^e, NHC(O)(CR^mRⁿ)NR^aR^c, NHC(O)NR^fR^g, (1-6C alkyl)-hetAr¹, (1-6C alkyl)-hetCyc¹, oxo, and C(O)O(1-6C alkyl).

[00115] Examples of R⁹ groups having the formula (1-6C)alkyl include methyl, ethyl, and propyl.

[00116] Examples of R⁹ groups having the formula NR^aR^b include groups where R^a is H or Me and R^b is H, methyl, ethyl, propyl, butyl, t-butyl, CH₂C(CH₃)₂OH, cyclopropyl, phenyl, or CH₂hetAr⁴. Examples of hetAr⁴ include 6 membered heteroaryl rings having 1-2 nitrogen atoms, for example pyridyl and pyrimidyl. Particular values of R⁹ when represented by NR^aR^b include NH₂ and NMe₂.

[00117] In other embodiments, R⁹ is a group having the formula NR^aR^b wherein R^a is H or (1-6C alkyl), and R^b is H, (1-6C alkyl), (1-6C fluoroalkyl), (1-6C alkyl)-O-(1-6C alkyl) or (1-6C alkyl)OH. Further particular values of R⁹ include NH₂, NHMe, NMe₂, NHCH(CH₃)CH₂F, NHCH₂CH₂OMe, NHCH₂CH₂OH and N(CH₃)CH₂CH₂OH.

[00118] Examples of R⁹ groups having the formula (1-6C alkyl)NR^aR^c include groups where R^a is H or Me and R^c is H, methyl, or cyclopropyl. Particular values of R⁹ when represented by (1-6C alkyl)NR^aR^c include CH₂NH₂ and CH₂CH₂NMe₂.

[00119] Examples of R⁹ groups having the formula OR^a include groups where R^a is H or (1-6C) alkyl. Particular mention is made of OH. Further mention is made of OMe.

[00120] Examples of R⁹ groups having the formula (1-6C alkyl)OR^a optionally substituted with an amino group include groups where R^a is H. Particular values of such substituents include CH₂OH. A further example of R⁹ is CH(NH₂)CH₂OH.

[00121] Examples of R⁹ groups having the formula C(O)NR^aR^c include groups where R^a is H or Me and R^c is (1-6C)alkyl, for example methyl. A particular value of R¹ is C(O)NHMe.

[00122] Examples of R⁹ groups having the formula C(O)(CR^xR^y)NR^aR^c include groups wherein R^x and R^y are independently H or methyl, R^a is H or methyl, and R^c is H or (1-6C)alkyl, for example methyl. In another embodiment, R^x and R^y together with the atom to which they are attached form a cyclopropyl ring. That is, CR^xR^y forms a cyclopropyl ring. Particular values of R⁹ include C(O)C(CH₃)₂NH₂, C(O)CH(CH₃)NH₂, C(O)CH₂NH₂, C(O)CH₂NMe₂, and C(O)C(cyclopropylidine)NH₂.

[00123] Examples of R⁹ groups having the formula NHC(O)R^e include groups wherein R^e is methyl.

[00124] Examples of R⁹ groups having the formula NHC(O)(CR^mRⁿ)NR^aR^e include groups wherein R^m and Rⁿ are independently H or methyl, R^a is H or Me, and R^e is H or Me. Particular values of R⁹ include NHC(O)CH₂NH₂, NHC(O)CH(CH₃)NH₂, and NHC(O)C(CH₃)₂NH₂.

[00125] Examples of R⁹ groups having the formula NHC(O)NR^fR^g include groups wherein R^f and R^g are independently H or Me. A particular value includes NHC(O)NH₂.

[00126] Examples of R⁹ groups having the formula (1-6C alkyl)-hetAr¹ include groups wherein hetAr¹ is a 6 membered heteroaryl having at least one nitrogen atom, for example a pyridyl group. Particular values of R⁹ include CH₂(pyrid-2-yl) and CH₂(pyrid-4-yl).

[00127] Examples of R⁹ groups having the formula (1-6C alkyl)-hetCyc¹ include groups wherein hetCyc¹ is a 5-6 membered ring having 1-2 nitrogen atoms. Particular values of hetCyc¹ include optionally substituted piperazinyl or pyrrolidinyl rings. In certain embodiments, hetCyc¹ is optionally substituted with OH or an alkyl group, for example methyl.

[00128] In certain embodiments, R⁹ is halogen. A particular example is fluoro.

[00129] In certain embodiments, R⁹ is CF₃.

[00130] In certain embodiments, R⁹ is CN.

[00131] In certain embodiments of Formula I, A is -Z(CH₂)_p(hetCyc^{2a}) wherein hetCyc^{2a} is optionally substituted with one or more R⁹ groups independently selected from halogen, (1-6C alkyl), C(O)O(1-6C alkyl) and -OR^a.

[00132] In certain embodiments, hetCyc^{2a} is optionally substituted with one or more R⁹ groups independently selected from F, methyl, C(O)₂Me, OH, and OMe.

[00133] In certain embodiments of Formula I, A is Z-hetCyc^{2b} wherein hetCyc^{2b} is optionally substituted with one or more R⁹ groups independently selected from halogen, (1-6C alkyl), and -OR^a.

[00134] In certain embodiments, hetCyc^{2b} is optionally substituted with one or more R⁹ groups independently selected from F, Me and OH.

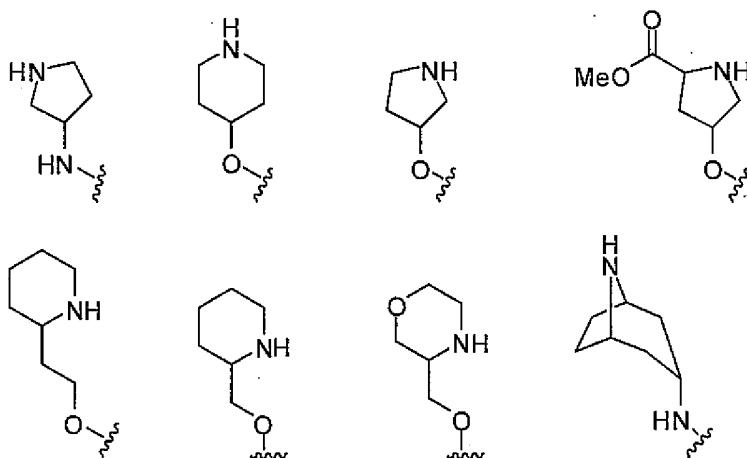
[00135] In certain embodiments, hetCyc^{2b} is unsubstituted.

[00136] In other embodiments, hetCyc^{2a} and hetCyc^{2b} are optionally substituted with one or more R⁹ groups independently selected from NH₂, NMe₂, Me, OH, CH₂OH, C(O)NHMe, CH₂NH₂, CH₂CH₂NH₂ and CO₂Me. Particular mention is made of NH₂.

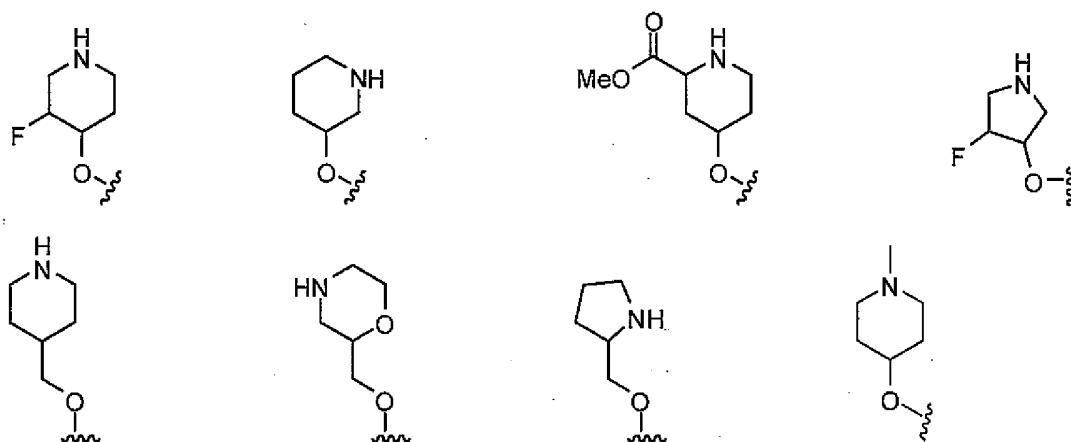
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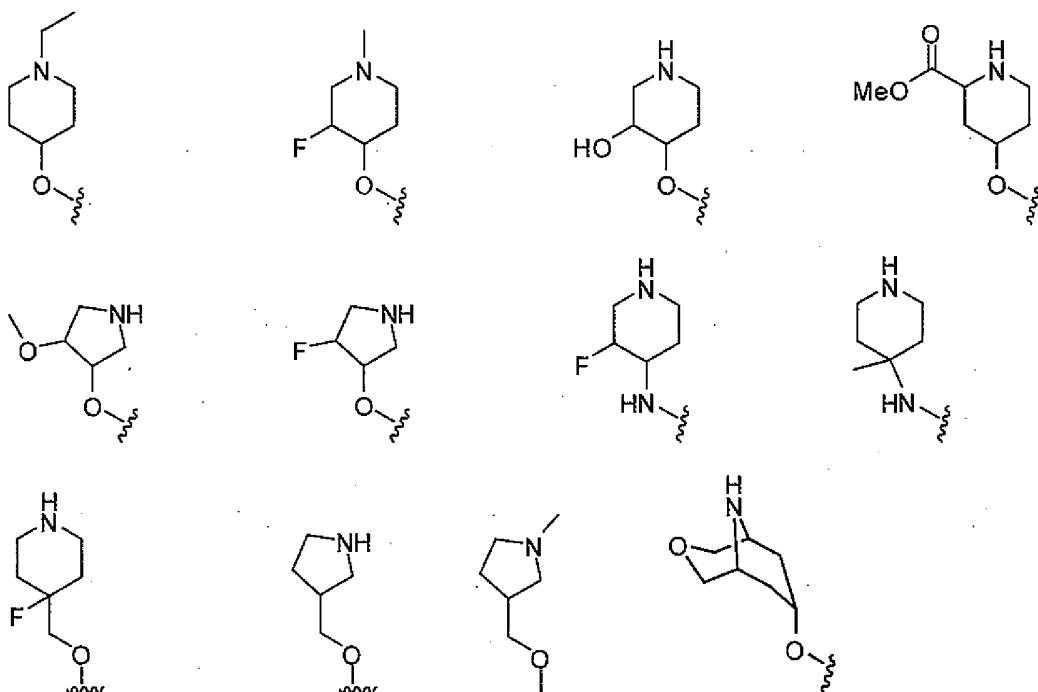
[00137] In other embodiments, hetCyc^{2a} and hetCyc^{2b} are optionally substituted with one or more R⁹ groups independently selected from NH-cyclopropyl, NH(t-butyl), NHMe, NHCH₂C(CH₃)₂OH, NHCH₂(pyrid-2-yl), NHCH₂(pyrid-4-yl), oxo, CH(NH₂)CH₂OH, C(O)C(CH₃)₂NH₂, C(O)CH(CH₃)NH₂, C(O)CH₂NH₂, C(O)CH₂NMe₂, C(O)C(cyclopropylidene)NH₂, CH₂CH₂NHMe, CH₂NMe₂, CH₂NH-cyclopropyl, CH₂NHMe, CH₂-(4-methylpiperazinyl), CH₂(3-hydroxypyrrolidinyl), NHC(O)Me, NHC(O)NH₂, NHC(O)CH₂NH₂, NHC(O)CH(CH₃)NH₂, NHC(O)C(CH₃)₂NH₂, CH₂(pyrid-2-yl), and CH₂(pyrid-4-yl).

[00138] Particular values of A when represented by the formula -Z(CH₂)_p(hetCyc^{2a}) or Z-hetCyc^{2b} include the structures:



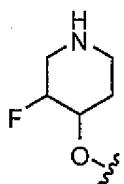
[00139] Additional values for the A group when represented by the formula -Z(CH₂)_p(hetCyc^{2a}) or Z-hetCyc^{2b} include the structures:





[00140] The values of A shown above include the *cis*- and *trans*- isomers where possible.

[00141] In certain embodiments of Formula I, A is -O-hetCyc^{2a}. In particular embodiments, hetCyc^{2a} is substituted with a fluoro group. In particular embodiments, hetCyc^{2a} is a piperidinyl ring. In particular embodiments, A is a group having the formula:



[00142] In particular embodiments, the A group is in the *trans*-configuration.

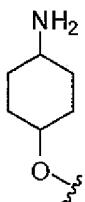
[00143] In certain embodiments, A is ZR¹⁰. In certain embodiments, Z is O. In certain embodiments, Z is N.

[00144] Particular values for R¹⁰ include straight chain and branched (1-6C alkyl) groups. In certain embodiments, R¹⁰ is substituted with NR'R". Particular mention is made of NH₂. A particular value for R¹⁰ is CH₂C(CH₃)₂CH₂NH₂. Additional values for R¹⁰ include CH₂C(CH₃)₂N(CH₃)₂ and CH₂CH₂NH₂.

[00145] Particular values for A when represented by ZR¹⁰ include -OMe, -OCH₂C(CH₃)₂CH₂NH₂, -OCH₂C(CH₃)₂N(CH₃)₂ and -OCH₂CH₂NH₂.

[00146] In certain embodiments, A is ZR¹¹. In certain embodiments, Z is O. In certain embodiments, A is N. In certain embodiments, R¹¹ is substituted with NR'R". In certain

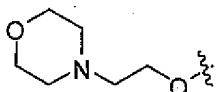
embodiments, R' and R" are independently selected from H and methyl. Particular mention is made of NH₂. Particular examples of R¹¹ include amino-substituted cyclopentyl and amino-substituted cyclohexyl rings. A particular value of A is:



- [00147] The examples of A when represented by ZR¹¹ include the *cis*- and *trans*-isomers.
- [00148] In certain embodiments, B is CN.
- [00149] In certain embodiments, B is H.
- [00150] In certain embodiments, B is OR^h.
- [00151] In certain embodiments, B is represented by OR^h wherein R^h is H.
- [00152] In certain embodiments, B is represented by OR^h wherein R^h is CF₃.
- [00153] Particular values for OR^h when R^h is represented by (1-6C)alkyl include OMe, OEt and O-(isobutyl).
- [00154] Particular values for OR^h when R^h is represented by -(1-6Calkyl)-(3-6C cycloalkyl) include -O-(1-6Calkyl)-cyclopropyl, for example -OCH₂-cyclopropyl.
- [00155] Particular values for OR^h when R^h is represented by -(1-6C alkyl)-O-(1-6C alkyl) include -OCH₂CH₂OMe and -OCH₂CH₂CH₂OMe.
- [00156] Particular values for OR^h when R^h is represented by -(1-6C alkyl)OH include -OCH₂CH₂OH.
- [00157] A particular value for OR^h when R^h is represented by -(1-6C alkyl)-S-(1-6C alkyl) includes -OCH₂CH₂CH₂SMe.
- [00158] Particular values for OR^h when R^h is represented by -(1-6C alkyl)NR'R" include groups wherein R' and R" are independently H or Me, for example, -OCH₂CH₂CH₂NH₂, -OCH₂CH₂NMe₂, and -OCH₂CH₂ CH₂NMe₂. A further example of OR^h includes -OCH₂CH₂NH₂.
- [00159] Particular values for OR^h when R^h is represented by hetCyc⁴ include groups wherein hetCyc⁴ is a 5-6 membered heterocyclic ring having 1-2 atoms independently selected from N and O. In certain embodiments, R^h is a 5-6 membered heterocycle having a ring oxygen atom, for example a tetrahydrofuryl or tetrahydropyran ring. Examples of OR^h include:

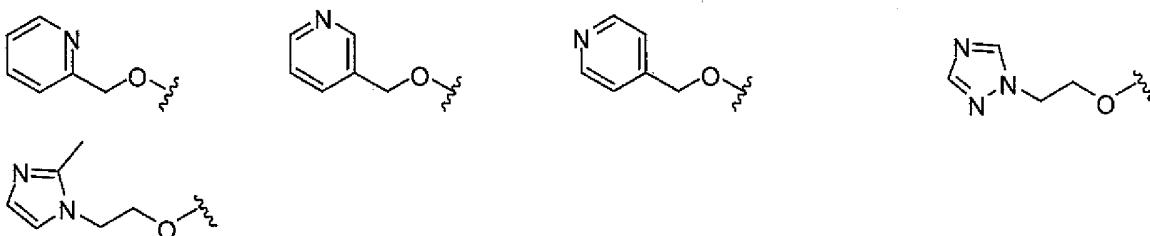


[00160] Particular values for OR^h when R^h is represented by (1-6C alkyl)hetCyc⁴ include groups wherein hetCyc⁴ is a 5-6 membered heterocyclic ring having 1-2 atoms independently selected from N and O. A particular example of OR^h includes the structure:



[00161] Particular values for OR^h when R^h is represented by (1-6C alkyl)aryl include groups wherein the aryl is a phenyl group, such as OCH_2Ph .

[00162] Particular values for OR^h when R^h is represented by (1-6C alkyl)-hetAr⁵ include groups wherein hetAr⁵ is a 5-6 membered heteroaryl ring having 1-3 nitrogen atoms. Examples include pyridyl, triazolyl and pyrazolyl rings. In certain embodiments, hetAr⁵ is substituted with a group selected from (1-6C) alkyl. Particular examples of OR^h include the structures:



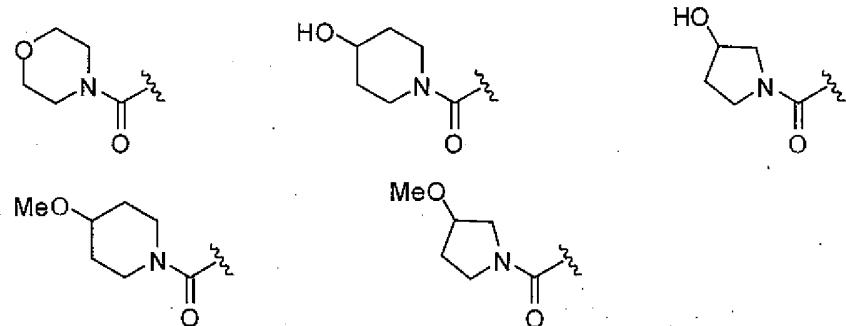
[00163] In certain embodiments of Formula I, B is OR^h wherein R^h is (1-6C alkyl)-O-(1-6C alkyl), hetCyc⁴ or -(1-6C alkyl)-(3-6C cycloalkyl).

[00164] In certain embodiments of Formula I, B is OR^h wherein R^h is (1-6C alkyl)-O-(1-6C alkyl), a 5-6 membered heterocycle having a ring oxygen atom, or - CH_2 (cyclopropyl).

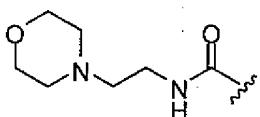
[00165] In certain embodiments, B is $C(O)NR^iR^j$. In certain embodiments, R^i is H. In certain embodiments, R^j is (1-6C alkyl), for example methyl. In other embodiments, R^j is (1-6C alkyl)O(1-6 alkyl), for example (1-6C alkyl)OMe. In other embodiments, R^j is (1-6C alkyl)OH for example (1-6C alkyl)OH. Particular values for B include - $C(O)NHMe$, - $C(O)NHCH_2CH_2OMe$, and - $C(O)NHCH_2CH_2OH$. A further example includes - $C(O)NMe_2$.

[00166] In certain embodiments, B is $C(O)$ -hetCyc³. Examples of hetCyc³ include 5-6 membered heterocyclic rings having 1-2 atoms independently selected from N and O. Particular values for B include the structures:

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[00167] In certain embodiments, B is C(O)(1-6C alkyl)hetCyc³. In certain embodiments, B is C(O)NH(1-6C alkyl)hetCyc³. Examples of hetCyc³ include 5-6 membered heterocyclic rings having 1-2 atoms independently selected from N and O. In certain embodiments, hetCyc³ is substituted with OH or OMe. A particular value for B includes the structure:



[00168] In certain embodiments, B is hetAr². Examples of hetAr² include 5-6 membered heteroaryl rings having 1-2 nitrogen atoms. In certain embodiments, hetAr² is substituted with -O(1-6C alkyl), such as methoxy. Particular values for B include 3-pyridyl, 4-pyridyl, and 4-methoxypyridyl-3-yl. Examples further include pyridyl groups optionally substituted with (1-6C)alkyl, for example methyl. A particular example includes 4-methylpyrid-3-yl. Additional examples of B when represented by hetAr² include pyrimidyl groups, such as 2-pyrimidyl and 5-pyrimidyl.

[00169] In certain embodiments, B is SR^k. In certain embodiments, R^k is a 3-6 membered carbocyclic ring. In other embodiments, R^k is -(1-6C alkyl)O(1-6C alkyl), e.g., (1-6C alkyl)OCH₃. Particular values for B include S-cyclohexyl and S(CH₂CH₂)OCH₃.

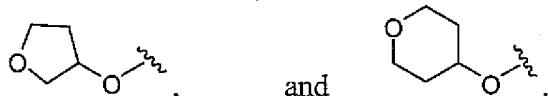
[00170] In certain embodiments, B is Ar¹. In certain embodiments, Ar¹ is phenyl which is unsubstituted or substituted with OH, O-(1-6C alkyl), C(O)₂(1-6C alkyl), or (1-6C alkyl)NR'R". Particular values for B include phenyl, hydroxyphenyl, 3-methoxyphenyl, 4-(methylamino)phenyl, or 4-(methoxycarbonyl)phenyl.

[00171] In certain embodiments, B is -(1-6C alkyl)NR'R". Particular values include CH₂NHMe and CH₂NMe₂.

[00172] In certain embodiments, B is -SO₂N(1-6C alkyl)₂, for example SO₂NMe₂.

[00173] In certain embodiments, B is (1-3C)alkyl. A particular value is ethyl.

[00174] In certain embodiments of Formula I, B is selected from OR^h, (1-3C)alkyl, hetAr² and hetCyc⁴. In certain embodiments, B is selected from -OCH₂CH₂OCH₃, -OCH₂CH₂OH, -OCH₂(cyclopropyl), ethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-methylpyrid-3-yl, 2-pyrimidyl, 5-pyrimidyl,

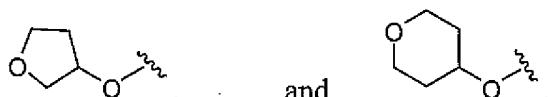


and

[00175] In certain embodiments of Formula I, B is selected from OR^h.

[00176] In certain embodiments, R^h is (1-6C alkyl)-O-(1-6C alkyl), (1-6Calkyl)-(3-6C cycloalkyl), -(1-6C alkyl)OH, or hetCyc⁴.

[00177] In certain embodiments of Formula I, B is selected from -OCH₂CH₂OCH₃, -OCH₂CH₂OH, -OCH₂(cyclopropyl),



and

[00178] In certain embodiments of Formula I, B is -OCH₂CH₂OCH₃.

[00179] In certain embodiments of Formula I, B is hetAr².

[00180] In certain embodiments, B is a pyridyl ring or a pyrimidyl ring.

[00181] In certain embodiments of Formula I, B is selected from 2-pyridyl, 3-pyridyl, 4-pyridyl, or 2-pyrimidyl.

[00182] In certain embodiments of Formula I, B is 3-pyridyl.

[00183] Compounds of Formula I include compounds wherein:

[00184] A is -Z-(CH₂)_p-(hetCyc^{2a}), -Z-(hetCyc^{2b}), Z-R¹⁰ or Z-R¹¹;

[00185] Z is O or NH;

[00186] p is 0, 1 or 2;

[00187] hetCyc^{2a} is a 5 or 6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, wherein hetCyc^{2a} is optionally substituted with one or more R⁹ groups;

[00188] hetCyc^{2b} is a 7-12 membered spirocyclic or bridged heterobicyclic ring system having 1-2 ring heteroatoms independently selected from N and O, wherein hetCyc^{2b} is optionally substituted with one or more R⁹ groups;

[00189] R¹⁰ is 1-6C alkyl or (1-6C alkyl)NR'R";

[00190] R¹¹ is (5-6C)cycloalkyl substituted with NR'R";

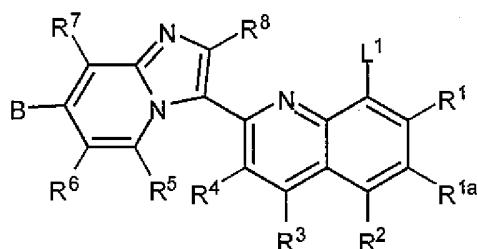
[00191] B is OR^h, (1-3C)alkyl, or pyridyl;

- [00192] R¹, R^{1a}, R², and R⁴ are independently H or F;
- [00193] R³ is H, F or hetAr³;
- [00194] R⁵, R⁶, R⁷ and R⁸ are independently H or F;
- [00195] each R⁹ is independently selected from halogen, C(O)O(1-6C alkyl), (1-6C alkyl), OH, and -O(1-6C alkyl);
- [00196] R^h is (1-6C alkyl)-O-(1-6C alkyl), a 5-6 membered heterocycle having a ring oxygen atom, or cyclopropylmethyl;
- [00197] hetAr³ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O; and
- [00198] R' and R" are independently H or (1-6C)alkyl.
- [00199] The term "halogen" as used herein includes F, Cl, Br, and I.
- [00200] The term "C₁-C₆ alkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms, respectively. Examples include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethylpropyl, 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, and 3,3-dimethyl-2-butyl.
- [00201] The term "-(1-6C alkyl)-(3-6C cycloalkyl)" refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to six carbon atoms, wherein one of the hydrogen atoms is replaced with a 3-6 membered cycloalkyl group.
- [00202] Compounds according to the present invention have been found to be class 3 receptor tyrosine kinase inhibitors and are useful in the treatment of cancers, such as hematological cancers (e.g., leukemias such as AML), breast cancer, colon cancer, gliomas, fibrosis (including liver fibrosis and lung fibrosis), and scleroderma.
- [00203] It will be appreciated that certain compounds according to the invention may contain one or more centers of asymmetry and may therefore be prepared and isolated in a mixture of isomers such as a racemic mixture, or in an enantiomerically pure form.
- [00204] It will further be appreciated that the compounds of Formula I or their salts may be isolated in the form of solvates, and accordingly that any such solvate is included within the scope of the present invention.

[00205] The compounds of Formula I include pharmaceutically acceptable salts thereof. In addition, the compounds of Formula I also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula I and/or for separating enantiomers of compounds of Formula I.

[00206] According to another aspect, the present invention provides a process for the preparation a compound of Formula I or a salt thereof as defined herein which comprises:

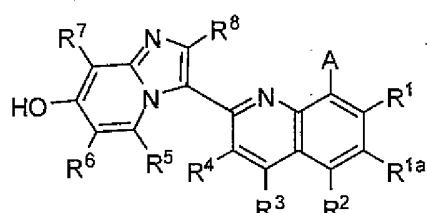
[00207] (a) for a compound of the Formula I wherein A is $-\text{NH}-(\text{CH}_2)_n(\text{hetCyc}^{2a})$, $-\text{NH}-(\text{hetCyc}^{2b})$, NHR^{10} or NHR^{11} , coupling a corresponding compound having the formula II



II

[00208] wherein L^1 represents a leaving group or atom, with a compound having the formula $\text{NH}_2(\text{CH}_2)_n(\text{hetCyc}^{2a})$, $\text{H}_2\text{N-hetCyc}^{2b}$, NH_2R^{10} or NH_2R^{11} , using a palladium catalyst and a ligand in the presence of a base; or

[00209] (b) for a compound of Formula I where B is OR^h , reacting a corresponding compound having the Formula III



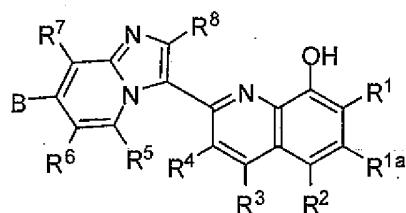
III

[00210] with a compound of the formula $\text{R}^h\text{-L}^2$ wherein L^2 represents a leaving group in the presence of a base; or

[00211] (c) for a compound of Formula I where B is OR^h , reacting a corresponding compound having the Formula III with a compound having the formula $\text{R}^h\text{-OH}$ in the presence of a coupling reagent; or

[00212] (d) for a compound of Formula I wherein A is $-\text{O}-(\text{CH}_2)_n\text{hetCyc}^{2a}$, $-\text{O-hetCyc}^{2b}$, OR^{10} or OR^{11} , reacting a corresponding compound having the formula IV

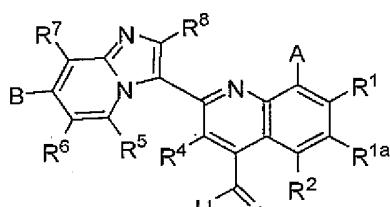
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**IV**

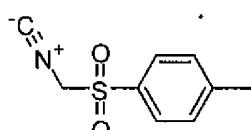
[00213] with a corresponding compound having the formula HO-(CH₂)_nhetCyc^{2a}, HO-hetCyc^{2b}, HOR¹⁰ or HOR¹¹ in the presence of a coupling agent and triphenylphosphine in a suitable solvent; or

[00214] e) for a compound of Formula I wherein A is -O-(CH₂)_nhetCyc^{2a}, reacting a compound of Formula IV with a compound having the formula MeSO₂-O(CH₂)_nhetCyc^{2a} in the presence of a base; or

[00215] f) for a compound of Formula I wherein R³ is hetAr³ and hetAr³ is oxazolyl, cyclizing a compound having the formula V

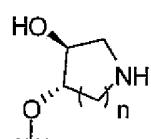
**V**

[00216] with a compound having the formula

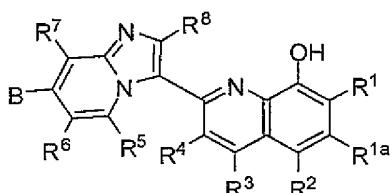


[00217] in the presence of a base; or

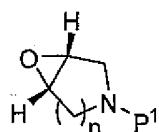
[00218] g) for a compound of Formula I wherein A is



[00219] and n is 1 or 2, reacting a corresponding compound having the formula IV

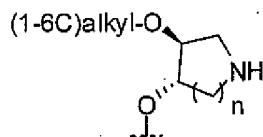
**IV**

[00220] with a compound having the formula

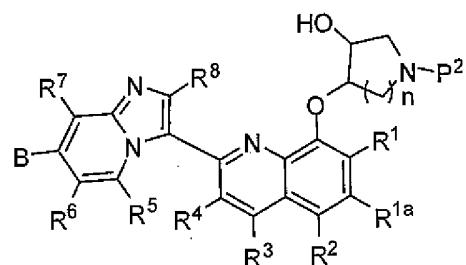


[00221] wherein n is 1 or 2 and P¹ is an amine protecting group, in the presence of a base; or

[00222] (h) for a compound of Formula I wherein A is:



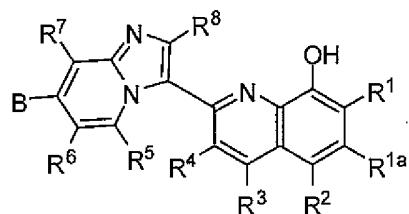
[00223] and n is 1 or 2, reacting a corresponding compound having the formula VII



VII

[00224] wherein n is 1 or 2, and P² is H or an amine protecting group, with a compound having the formula (1-6C alkyl)L³ where L³ is a leaving group or atom in the presence of a base; or

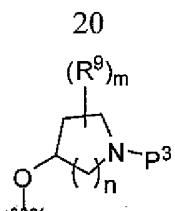
[00225] (i) for a compound of Formula I wherein A is O-(1-6C alkyl)NR'R'', reacting a compound having the formula IV



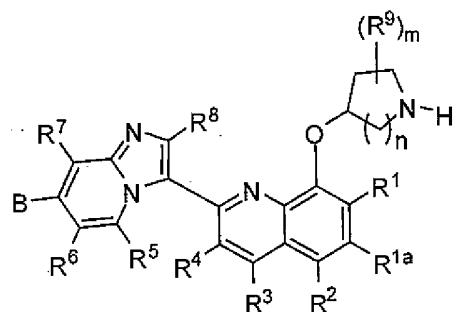
IV

[00226] with a compound having the formula L⁴-(1-6C alkyl)NR'R'' where L⁴ is a leaving group or atom, in the presence of a base and optionally in the presence of a phase transfer catalyst; or

[00227] (j) for a compound of Formula I wherein A is:



[00228] and n is 1 or 2, P³ is (1-6C)alkyl, reacting a corresponding compound having the formula VIII



[00229] with a compound having the formula HC(O)P^{3a} where P^{3a} is H or (1-6C)alkyl, in the presence of a reducing agent; and

[00230] removing any protecting group or groups and optionally forming a salt.

[00231] Referring to method (a), the leaving atom L¹ may be, for example a halogen atom such as Br or I. Alternatively, L¹ can be a leaving group, such as a hydrocarbonylsulfonyloxy group, for example, a triflate group, or an arylsulfonyloxy group or an alkylsulfonyloxy group, such as a mesylate or a tosylate group. Suitable palladium catalysts include Pd(0) and Pd(II) catalysts, for example Pd₂(dba)₃ and Pd(OAc)₂. Suitable ligands include rac-BINAP or DIPHOS. The base may be, for example, an alkali metal carbonate or alkoxide, such as for example cesium carbonate or sodium tert-butoxide. Convenient solvents include aprotic solvents such as ethers (for example tetrahydrofuran or p-dioxane) or toluene. The coupling of a compound of formula (II) with HNR¹⁰R¹¹ can be conveniently performed at a temperature between 0 °C and reflux, and more particularly at reflux.

[00232] Referring to method (b), the leaving atom L¹ may be, for example a halogen atom such as Br, Cl or I. Alternatively, L¹ can be a leaving group, for example an arylsulfonyloxy group or an alkylsulfonyloxy group, such as a mesylate or a tosylate group. The base may be, for example, an alkali metal hydride or carbonate, such as sodium hydride, potassium hydride, sodium carbonate, potassium carbonate or cesium carbonate. Convenient solvents include aprotic solvents such as ethers (for example tetrahydrofuran or p-dioxane), DMF, or acetone. The reaction can be conveniently performed at a temperature ranging from -78 to 100 °C.

[00233] Referring to method (c), the coupling reagent may be any suitable reagent(s) known to those skilled in the art, for example, DEAD and PPh₃. Convenient solvents include aprotic solvents such as ethers (for example tetrahydrofuran). The reaction can be conveniently performed at a temperature ranging from -78 to 100 °C.

[00234] Referring to method (d), the coupling reagent may be any suitable reagent(s) known to those skilled in the art, for example, DEAD and PPh₃. Convenient solvents include aprotic solvents such as ethers (for example tetrahydrofuran). The reaction can be conveniently performed at a temperature ranging from -78 to 100 °C.

[00235] Referring to method (e), the base may be, for example, an alkali metal hydride or carbonate, such as sodium hydride, potassium hydride, sodium carbonate, potassium carbonate or cesium carbonate. Convenient solvents include aprotic solvents such as ethers (for example tetrahydrofuran or p-dioxane), dimethylformamide, dimethylacetamide, or acetone. The reaction can be conveniently performed at a temperature ranging from ambient temperature to 100 °C.

[00236] Referring to method (f), the base may be, for example, an alkali metal hydride or carbonate, such as sodium hydride, potassium hydride, sodium carbonate, potassium carbonate or cesium carbonate. Convenient solvents include alcohols such as methanol. The reaction can be conveniently performed at a temperature ranging from ambient temperature to 100 °C.

[00237] Referring to method (g), the base may be, for example, an alkali metal hydride or carbonate, such as sodium hydride, potassium hydride, sodium carbonate, potassium carbonate or cesium carbonate. Convenient solvents include aprotic solvents such as ethers (for example tetrahydrofuran or p-dioxane), dimethylformamide, dimethylacetamide, or acetone. The reaction can be conveniently performed at a temperature ranging from ambient temperature to 100 °C.

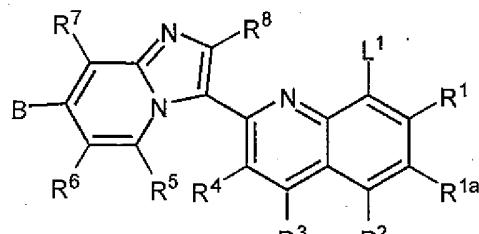
[00238] Referring to method (h), the base may be, for example, an alkali metal hydride, such as sodium hydride, potassium hydride, or lithium hydride. Convenient solvents include aprotic solvents such as ethers (for example tetrahydrofuran or p-dioxane), dimethylformamide, dimethylacetamide, or acetone. The leaving atom L³ may be, for example a halogen atom such as Br, Cl or I. Alternatively, L³ can be a leaving group, for example an arylsulfonyloxy group or an alkylsulfonyloxy group, such as a mesylate or a tosylate group.

[00239] Referring to method (i), the base may be, for example, an alkali metal hydroxide, such as sodium hydroxide, potassium hydroxide, lithium hydroxide or cesium hydroxide. Convenient solvents include aprotic solvents such as ethers (for example tetrahydrofuran or p-dioxane), dimethylformamide, dimethylacetamide, or acetone. The leaving atom L⁴ may be, for example a halogen atom such as Br, Cl or I. Alternatively, L⁴ can be a leaving group, for example an arylsulfonyloxy group or an alkylsulfonyloxy group, such as a mesylate or a tosylate group. The reaction is optionally performed in the presence of a phase transfer catalyst such as tetrabutylammonium iodide. The reaction can be conveniently performed at a temperature ranging from ambient temperature to 100 °C.

[00240] Referring to method (j), suitable reducing agents include borohydride reagents such as sodium triacetoxyborohydride or sodium cyanoborohydride.

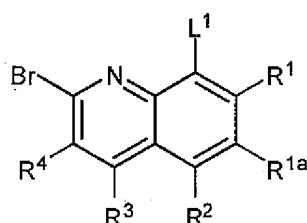
[00241] Suitable amine protecting groups for the above methods include any convenient amine protecting group, for example as described in Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", John Wiley & Sons, Inc. Examples of amine protecting groups include acyl and alkoxy carbonyl groups, such as t-butoxycarbonyl (BOC).

[00242] A compound of Formula II

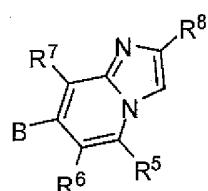


II

[00243] can be prepared by reacting corresponding 2,8-dibromoquinoline having the formula

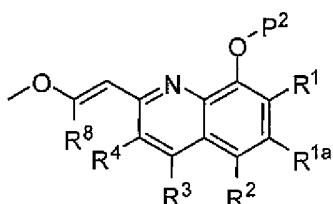


[00244] with a corresponding compound having the formula



[00245] using a palladium catalyst (such as Pd(PPh₃)₄, Pd₂(dba)₃ or Pd(OAc)₂) and a palladium ligand (for example rac-BINAP or DIPHOS) in the presence of a suitable base, for example an alkali metal carbonate or alkoxide base (e.g., cesium carbonate, potassium carbonate, or sodium tert-butoxide) in a suitable solvent (such as toluene or dioxane) at a temperature ranging from about ambient temperature to reflux.

[00246] A compound of Formula IV can be prepared by reacting a compound having the formula



[00247] wherein P² represents an alcohol protecting group, such as t-butyldimethylsilyl, with a compound having the formula



[00248] in the presence of N-bromosuccinimide or N-chlorosuccinimide in a suitable solvent (such as THF).

[00249] The compounds of the formulas (II), (III) and (IV) are believed to be novel and are provided as further aspects of the invention.

[00250] The ability of test compounds to act as PDGFR inhibitors may be demonstrated by the assay described in Example A.

[00251] The ability of test compounds to act as FLT3 inhibitors may be demonstrated by the assay described in Example B.

[00252] Compounds of Formula I are useful for treating diseases and disorders mediated by class 3 and/or class 5 receptor tyrosine kinases. In particular embodiments, compounds of this invention are inhibitors of one or more of the class 3 receptor tyrosine kinases, for example PDGFR and FLT3. For example, compounds of this invention are useful in the treatment fibrosis (including lung, liver and kidney fibroses), scleroderma, and cancers, including hematological malignancies.

[00253] As used herein, the term treatment includes prophylaxis as well as treatment of an existing condition.

[00254] Examples of hematological malignancies include, for instance, leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma--for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma (MM).

[00255] Particular examples of PDGFR-driven or dependent cancers which may be treated with compounds of this invention include dermatofibrosarcoma protuberans (DFSB), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), glioblastoma multiforme (GBM) and gastrointestinal stromal tumors (GIST).

[00256] FLT3 inhibitors may also be useful for treating immune related disorders such as bone marrow transplant rejection, solid organ rejection after transplant, ankylosing spondylitis, arthritis, aplastic anemia, Behcet's disease, Graves' disease, hemolytic anemia, hyper IgE syndrome, idiopathic thrombocytopenia purpura (ITP), multiple sclerosis (MS), rheumatoid arthritis, Wegener's granulomatosis, type 1 diabetes mellitus, Myasthenia gravis, and psoriasis.

[00257] Particular compounds of this invention are inhibitors of Pim-1 and therefore are useful in treating diseases and disorders mediated by Pim-1, such as cancers such as hematological cancers.

[00258] Accordingly, another aspect of this invention provides a method of treating diseases or medical conditions in a mammal mediated by a class 3 and/or class 5 receptor tyrosine kinase, comprising administering to said mammal one or more compounds of Formula I or a pharmaceutically acceptable salt or prodrug thereof in an amount effective to treat or prevent said disorder.

[00259] Another aspect of this invention provides a method of treating diseases or medical conditions in a mammal mediated by Pim-1, comprising administering to said mammal one or more compounds of Formula I or a pharmaceutically acceptable salt or prodrug thereof in an amount effective to treat or prevent said disorder.

[00260] The phrase "effective amount" means an amount of compound that, when administered to a mammal in need of such treatment, is sufficient to (i) treat or prevent a particular disease, condition, or disorder mediated by a class 3 receptor tyrosine kinase, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) prevent or delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

[00261] The amount of a compound of Formula I that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

[00262] As used herein, the term "mammal" refers to a warm-blooded animal that has or is at risk of developing a disease described herein and includes, but is not limited to, guinea pigs, dogs, cats, rats, mice, hamsters, and primates, including humans.

[00263] Compounds of the present invention can be used in combination with one or more additional drugs, for example an anti-inflammatory compound, anti-fibrotic compound or a chemotherapeutic that works by the same or by a different mechanism of action.

[00264] Compounds of the invention may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or vasculature, or transdermally or dermally. The compounds may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. If parenteral administration is desired, the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the invention.

[00265] According to another aspect, the present invention provides a pharmaceutical composition, which comprises a compound of Formula I or a pharmaceutically acceptable salt thereof, as defined hereinabove. In one embodiment, the pharmaceutical composition includes the compound of Formula I together with a pharmaceutically acceptable diluent or carrier.

[00266] According to another aspect, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in therapy, such as the treatment of a class 3 receptor tyrosine kinase-mediated condition.

- [00267] In certain embodiments, the invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.
- [00268] In certain embodiments, the invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of fibrosis.
- [00269] In certain embodiments, the invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of scleroderma.
- [00270] According to another aspect, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in therapy, such as the treatment of a Pim-1-mediated condition.
- [00271] According to a further aspect, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament to treat a class 3 receptor tyrosine kinase-mediated condition.
- [00272] According to a further aspect, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament to treat a Pim-1-mediated condition.

Examples

[00273] The following examples illustrate the invention. In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Lancaster, TCI or Maybridge, and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF), dichloromethane (DCM, methylene chloride), toluene, and dioxane were purchased from Aldrich in Sure seal bottles and used as received.

[00274] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00275] ^1H NMR spectra were obtained as CDCl_3 , CD_3OD , D_2O or d_6 -DMSO solutions (reported in ppm), using tetramethylsilane (0.00 ppm) or residual solvent (CDCl_3 : 7.25 ppm; CD_3OD : 3.31 ppm; D_2O : 4.79 ppm; d_6 -DMSO: 2.50 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

Example ACellular PDGFR Assay

[00276] The ability of compounds of this invention to inhibit PDGF-induced PDGFR phosphorylation was assessed by using mouse NIH3T3 cells.

[00277] 25,000 cells in DMEM supplemented with 10% fetal bovine serum were added to each well of a black 96-well cell culture plate. Plates were incubated in a 37°C/5% CO₂ incubator for 6-8 hours. Plates were then washed and incubated with serum-free DMEM, and the cells were returned to the 37 °C/5% CO₂ incubator for 16-20 hours.

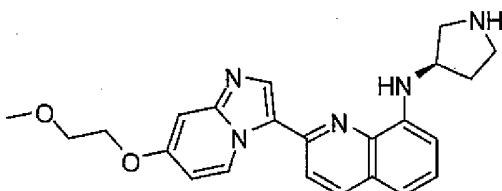
[00278] Compound test solutions were added at a final concentration of 0.5% DMSO, and the cells were incubated in a 37 °C/5% CO₂ incubator for 1 hour. PDGF-BB ligand was then added (75 ng/mL) and incubated for 15 minutes. Cells were washed with PBS and fixed in 3.7% formaldehyde in PBS for 10 minutes. This was followed by washing in PBS/0.2% Triton X-100 and permeabilizing in 100% MeOH for 10 minutes. Cells were blocked in Odyssey blocking buffer (LI-COR Biosciences) for 1 hour. Antibodies to phosphorylated PDGFR β and total PDGFR β were added to the cells and incubated for 3 hours. After washing with PBS/0.2% TritonX-100, the cells were incubated with fluorescently-labeled secondary antibodies (goat anti-rabbit IgG-IRDye800 and goat anti-mouse IgG-Alexa Fluor 680) for an additional hour. Cells were then washed with PBS and analyzed for fluorescence at both wavelengths using the Odyssey Infrared Imaging System (LI-COR Biosciences). Phosphorylated PDGFR signal was normalized to total PDGFR signal. Compounds of this invention had IC₅₀'s values less than 10 μ M in this assay.

Example BCellular FLT3 Assay

[00279] The inhibition of FLT3 ligand (FL)-induced phosphorylated FLT3 in human RS4;11 cells was measured as follows. Cells were plated in 96-well V-bottom plates in RPMI/10%FCS at a concentration of 1 million cells/well. Diluted compounds were added at a final concentration of 0.5% DMSO for one hour. FL was added at a final concentration of 50 ng/ml. After a 15 minute incubation, the cells were pelleted by centrifugation and resuspended in lysis buffer. Phospho-FLT3 was detected by standard ELISA procedure (R&D Systems; DYC368). Briefly, after 20 minutes on ice, the lysate was added to 96-well plates coated with capture antibody to total FLT3. Phospho-FLT3 was detected by the addition of antibody to phospho-tyrosine conjugated to HRP. After addition of substrate and stop solution, the signal

was read at A450. Compounds of this invention had IC₅₀'s values less than 10 μM in this assay.

Example 1



(R)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-N-(pyrrolidin-3-yl)quinolin-8-amine

[00280] Step 1A: Preparation of 2-chloro-4-(2-methoxyethoxy)pyridine: A mixture of 2-chloro-4-nitropyridine (43.6 g, 275.0 mmol) and 2-methoxyethanol (325.6 ml, 425 mmol) was cooled to 0°C. Potassium 2-methylpropan-2-olate (35.73 g, 302.5 mmol) was added and the resulting mixture was stirred while warming to ambient temp over 2 hours. The reaction mixture was concentrated under reduced pressure followed by dilution with 500 ml of water. The resulting mixture was extracted twice with 250 ml of dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to produce the desired compound as a golden oil (50.2 g, 97 % yield) MS APCI (+) m/z 188 and 189.9 (M+1 of each isotope) detected.

[00281] Step 1B: Preparation of 4-(2-methoxyethoxy)pyridin-2-amine: A steady stream of nitrogen was passed through a mixture of 2-chloro-4-(2-methoxyethoxy)pyridine (50.17 g, 267.4 mmol), Pd₂dba₃ (4.897 g, 5.348 mmol), XPHOS (5.099 g, 10.70 mmol) and tetrahydrofuran (445.7 ml) for 10 minutes. To the resulting degassed mixture was added lithium bis(trimethylsilyl)amide (561.5 ml, 561.5 mmol). After addition, the resulting mixture was heated to 60°C for 18 hours. The reaction was cooled to ambient temperature and diluted with 1 N hydrochloric acid (200 mL). The resulting solution was washed twice with 500 ml of methyl-tert-butyl ether. The pH of the aqueous layer was taken to 11 with 6 N NaOH and was extracted with dichloromethane (3 x 500 ml). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to yield title compound. (35 g, 78 % yield) MS APCI (+) m/z 169 (M+1) detected.

[00282] Step 1C: Preparation of 7-(2-methoxyethoxy)imidazo[1,2-a]pyridine: A mixture of 4-(2-methoxyethoxy)pyridin-2-amine (20.0 g, 119 mmol), 2-chloroacetaldehyde (32.2 ml, 250 mmol) and tetrahydrofuran (100 mL) were heated in a sealed tube to 75°C over 3 days. The reaction mixture was concentrated under reduced pressure and dissolved in ethyl acetate. The resulting solution was washed twice sodium bicarbonate. The combined organic

layers were dried over MgSO₄ and concentrated under reduced pressure to yield title compound (23.5 g, quantitative yield) MS APCI (+) m/z 193 (M+1) detected.

[00283] Step 2A: Preparation of N-(2-bromophenyl)cinnamamide: To a mixture of 2-bromobenzylamine (200.0 g, 1163 mmol), pyridine (188.1 ml, 2325 mmol) and dry dichloromethane (1000 ml) at 0°C was added slowly cinnamoyl chloride (193.7 g, 1163 mmol). The resulting mixture was stirred while warming to ambient temperature overnight. The resulting mixture was washed with sodium bicarbonate (1000 ml), 10 % sodium bisulfate (1000 ml), sodium bicarbonate (1000 ml) and brine (1000 ml). The organic layer was dried over MgSO₄ and concentrated under reduced pressure to yield title compound as a solid (172.3 gm, 98% yield) MS ESI (+) m/z 224 and 226 (M+1 of each isotope) detected.

[00284] Step 2B: Preparation of 8-bromoquinolin-2(1H)-one: A mixture of N-(2-bromophenyl)cinnamamide (172.3 g, 570.3 mmol), aluminum chloride (456 g, 342 mmol) and chlorobenzene (1000 ml) were allowed to stir at 100°C for 7 hours followed by cooling to ambient temperature overnight. The resulting mixture was poured onto 2 kg of ice and was allowed to warm to ambient temperature over 1 hour. The resulting mixture was extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The resulting solids were triturated with 1000 ml hexanes. The solids were vacuum dried to yield title compound. (83 g, 65 % yield) MS ESI (+) m/z 224 and 226 (M+1 of each isotope) detected.

[00285] Step 2C: Preparation of 2,8-dibromoquinoline: A mixture of 8-bromoquinolin-2(1H)-one (5 g, 22 mmol) and phosphoryl tribromide (13 g, 45 mmol) was heated to 140°C for three hours. The resulting mixture was poured onto 100 g of ice and 100 ml water. The mixture was stirred for 1 hour and the resulting solids were filtered to yield the title compound. (5.1 g, 80 % yield) MS APCI (+) 286, 288, and 290 (M+1 of each isotope combination) detected.

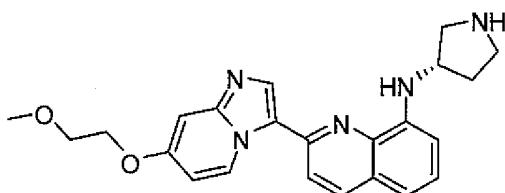
[00286] Step 2D: Preparation of 8-bromo-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline: A mixture of 2,8-dibromoquinoline (22.4 g, 78.0 mmol), 7-(2-methoxyethoxy)imidazo[1,2-a]pyridine (15.0 g, 78.0 mmol), Pd(PPh₃)₄ (4.51 g, 3.90 mmol), K₂CO₃ (21.6 g, 156 mmol) and Pd(OAc)₂ (0.876 g, 3.90 mmol), dioxane (312 mL) and water (3 ml) was heated to 100°C for 18 hours. The resulting mixture was diluted with dichloromethane (500 ml) and filtered. The filtrate was concentrated under reduced pressure and to the resulting oil was added ethyl acetate (100 ml) and methyl tert-butyl ether (100 ml).

The resulting mixture was stirred overnight. Filtration to collect the resulting solids yielded the title compound (22.2 g, 72 % yield). MS ESI (+) m/z 398 and 400 (M+1 of each isotope) detected.

[00287] Step 2E: Preparation of (S)-tert-butyl 3-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ylamino)pyrrolidine-1-carboxylate: A stream of argon was passed through a mixture of 8-bromo-2-(7-(2-methoxyethoxy)-imidazo[1,2-a]pyridin-3-yl)quinoline (0.100 g, 0.2511 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (0.05537 ml, 0.3264 mmol), Cs₂CO₃ (0.1145 g, 0.3515 mmol), Pd(OAc)₂ (0.01127 g, 0.05022 mmol) and rac-BINAP (0.01564 g, 0.02511 mmol) in toluene (1 mL) for 15 minutes. The mixture was heated to 100°C for 18 hours. The mixture was then allowed to cool to ambient temperature and dichloromethane was added. After stirring 30 minutes, the resulting mixture was filtered and the filtrate was concentrated to yield the title compound as an oil. MS APCI (+) m/z 504.1 (M+1) detected.

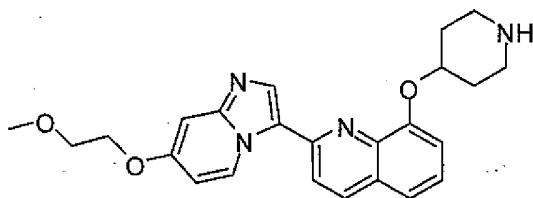
[00288] Step F: Preparation of (R)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-N-(pyrrolidin-3-yl)quinolin-8-amine: To a solution of (S)-tert-butyl 3-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ylamino)pyrrolidine-1-carboxylate (0.127 g, 0.252 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.389 ml, 5.04 mmol). The resulting mixture was stirred for 2 hours at ambient temperature. The dichloromethane reaction mixture was concentrated under reduced pressure and then diluted with dichloromethane. The resulting solution was washed twice with saturated sodium bicarbonate and twice with a brine solution. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification via flash column chromatography (40:1 CH₂Cl₂/MeOH to 20:1 CH₂Cl₂/MeOH to 10:1 CH₂Cl₂/MeOH) produced the title compound (53 mg, 52 % Yield). MS APCI (+) m/z 404.3 (M+1) detected.

Example 2



(S)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-N-(pyrrolidin-3-yl)quinolin-8-amine

[00289] Prepared according to the procedure for Example 1 using (S)-tert-butyl 3-aminopyrrolidine-1-carboxylate in place of (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate. MS APCI (+) m/z 404.3 (M+1) detected.

Example 32-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(piperidin-4-yloxy)quinoline

[00290] Step A: 8-(tert-butyldimethylsilyloxy)quinoline-2-carbaldehyde: 8-
Hydroxyquinoline-2-carbaldehyde (5.00 g, 28.9 mmol) and imidazole (4.32 g, 63.5 mmol) was dissolved in dichloromethane (50 mL) under an atmosphere of dry N₂. The reaction mixture was then cooled to 0 °C and tert-butylchlorodimethylsilane (4.94 g, 31.8 mmol) was added. The reaction was stirred overnight at ambient temperature, and then partitioned between dichloromethane and water. The organic layer was washed with water and aqueous saturated NaHCO₃, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification via flash chromatography (2:1 Hexanes/dichloromethane followed by 1:1 hexanes/dichloromethane) provided 6.50 g, 78% of the desired product as an oil.

[00291] Step B: (E)-8-(tert-butyldimethylsilyloxy)-2-(2-methoxyvinyl)quinoline:
Methoxymethyl triphenylphosphonium chloride (3.94 g, 11.5 mmol) was suspended in anhydrous THF (25 mL) under an atmosphere of dry N₂. After cooling to 0 °C, potassium tert-butoxide (1.41 g, 12.5 mmol) was added. The solution was stirred at 0 °C for 5 minutes, then warmed to ambient temperature. After 15 minutes 8-(tert-butyldimethylsilyloxy)quinoline-2-carbaldehyde (3.00 g, 10.4 mmol) was added. The reaction was stirred at ambient temperature overnight, and then concentrated under vacuum. Diethyl ether (200 mL) was added, and the mixture was stirred at ambient temperature for 1 hour and then filtered. The precipitate was washed with diethyl ether and the filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in diethyl ether (50 mL) to which hexanes (50 mL) was added. The mixture was stirred for 1 hour and then filtered. The filtrate was concentrated under vacuum to give 3.12 g, 95% of the desired product as a mixture of cis-trans isomers.

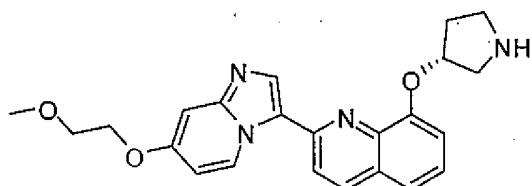
[00292] Step C: 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol: (E)-8-(tert-butyldimethylsilyloxy)-2-(2-methoxyvinyl)quinoline (1.90 g, 6.02 mmol) was dissolved in a solution of THF (20 mL) and water (3 mL). N-bromosuccinimide (1.13, 6.32 mmol) was added to the reaction mixture. After the reaction was judged to be complete (monitored by MS), 4-(2-methoxyethoxy)pyridin-2-amine 1.01 g, 6.02 mmol) was added. The reaction was then heated to reflux for 5 hours and then cooled to ambient temperature. To the reaction

mixture was added 10 ml of 1.0 M tetrabutylammonium fluoride in THF. The reaction mixture was stirred at ambient temperature for 1 hour and then diluted with water. The mixture was extracted with 1:4 isopropyl acetate:dichloromethane. The combined organic phase was dried (sodium sulfate), filtered and condensed under reduced pressures. The residue was purified by flash chromatography, eluting with gradient from 100 % EtOAc to 10 % MeOH (w/ 6% NH₄OH)/EtOAc to obtain 700 mg of the desired product as a red solid.

[00293] Step D: tert-butyl 4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: 2-(7-(2-Methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (0.030 g, 0.0895 mmol), tert-butyl 4-hydroxypiperidine-1-carboxylate (0.0198 g, 0.0984 mmol), triphenylphosphine (0.0352 g, 0.134 mmol) and diethyl azodicarboxylate (0.0211 ml, 0.134 mmol) were combined in anhydrous THF (1 mL). The reaction mixture was stirred overnight at ambient temperature, then diluted with EtOAc and washed with saturated NaHCO₃ and brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (dichloromethane followed by 40:1 dichloromethane/MeOH) which provided 29.0 mg of the desired product as a brown residue.

[00294] Step E: 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(piperidin-4-yloxy)quinoline: Trifluoroacetic acid 0.0862 ml, 1.12 mmol) was added to a solution of tert-butyl 4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (0.029 g, 0.0559 mmol) in dichloromethane (0.50 mL). After stirring overnight at ambient temperature, the reaction mixture was concentrated under reduced pressure and partitioned between dichloromethane and saturated NaHCO₃. The organic layer was washed with saturated NaHCO₃ and brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (40:1 dichloromethane /MeOH followed by 5:1 dichloromethane/MeOH followed by 2:1 dichloromethane/MeOH) provided 10.0 mg of the desired compound. MS APCI (+) m/z 419.2 (M+1) detected.

Example 4

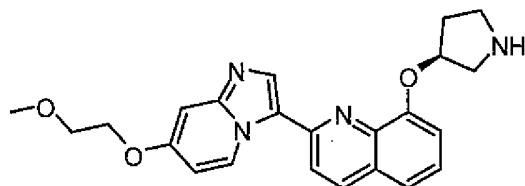


(R)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(pyrrolidin-3-yloxy)quinoline

33

[00295] Prepared according to the procedure for Example 3 using (S)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate in place of tert-butyl 4-hydroxypiperidine-1-carboxylate. MS APCI (+) m/z 405.2 (M+1) detected.

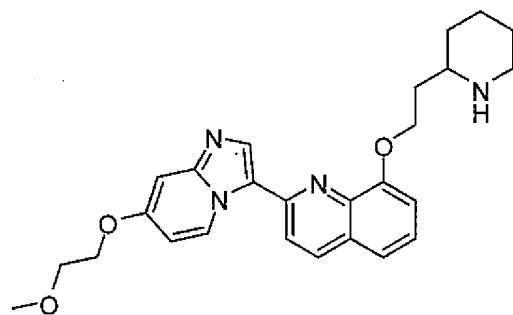
Example 5



(S)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(pyrrolidin-3-yloxy)quinoline

[00296] Prepared according to the procedure for Example 3 using (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate in place of tert-butyl 4-hydroxypiperidine-1-carboxylate. MS APCI (+) m/z 405.2 (M+1) detected.

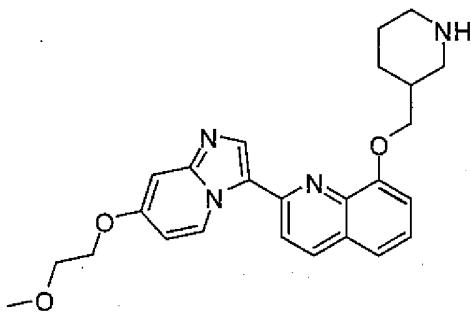
Example 6



2-(7-(2-Methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(2-(piperidin-2-yl)ethoxy)quinoline

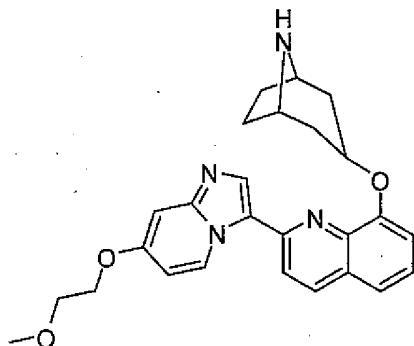
[00297] Prepared according to the procedure for Example 3 using the appropriate amine-protected 2-(piperidin-2-yl)ethanol. MS APCI (+) m/z 447.3 (M+1) detected.

Example 7



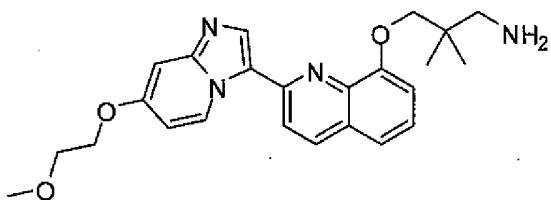
2-(7-(2-Methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(piperidin-3-ylmethoxy)quinoline

[00298] Prepared according to the procedure for Example 3 using the appropriate amine-protected piperidin-3-ylmethanol. MS APCI (+) m/z 433.3 (M+1) detected.

Example 8

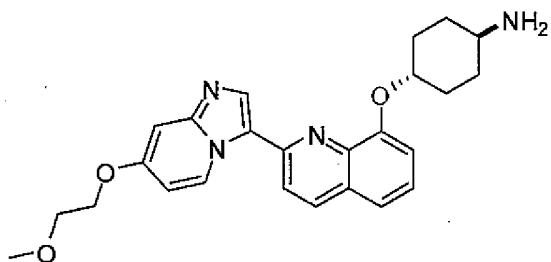
8-(8-Azabicyclo[3.2.1]octan-3-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00299] Prepared according to the procedure for Example 3 using the amine-protected 8-azabicyclo[3.2.1]octan-3-ol. MS APCI (+) m/z 445.2 (M+1) detected.

Example 9

3-(2-(7-(2-Methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine

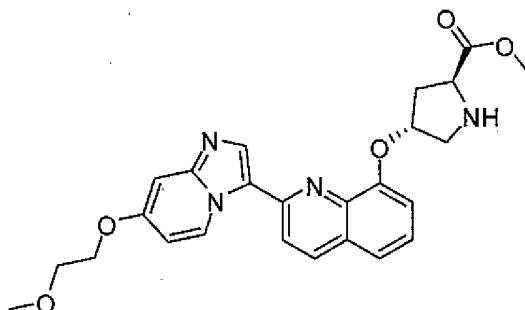
[00300] Prepared according to the procedure for Example 3 using the appropriate amine-protected 3-amino-2,2-dimethylpropan-1-ol. MS APCI (+) m/z 421.2 (M+1) detected.

Example 10

(1R, 4R)-4-(2-(7-(2-Methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)cyclohexanamine

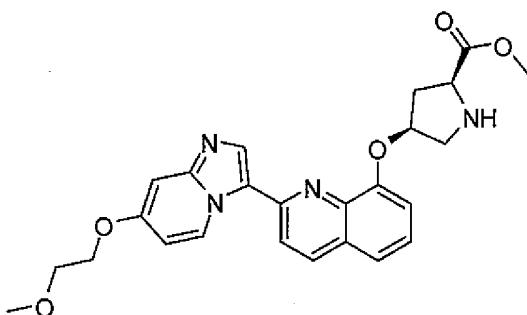
[00301] Prepared according to the procedure for Example 3 using the appropriate amine-protected (1R,4R)-4-aminocyclohexanol. MS APCI (+) m/z 433.1 (M+1) detected.

35

Example 11

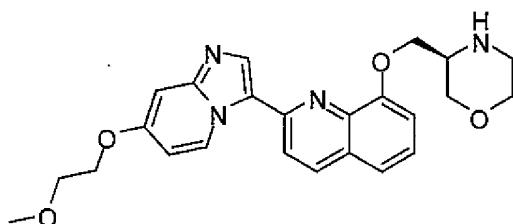
(2S,4R)-Methyl 4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-2-carboxylate

[00302] Prepared according to the procedure for Example 3 using the appropriate amine-protected (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate. MS APCI (+) m/z 463.2 (M+1) detected.

Example 12

(2S,4S)-Methyl 4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-2-carboxylate

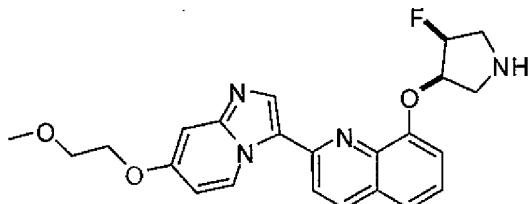
[00303] Prepared according to the procedure for Example 3 using the appropriate amine-protected (2S,4S)-methyl 4-hydroxypyrrolidine-2-carboxylate. MS APCI (+) m/z 463.2 (M+1) detected.

Example 13

(S)-3-((2-(7-(2-Methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)methyl)morpholine

[00304] Prepared according to the procedure for Example 3 using the appropriate amine-protected (R)-morpholin-3-ylmethanol. MS ESI (+) m/z 435.2 (M+1) detected.

Example 14



8-((cis)-4-fluoropyrrolidin-3-yl)oxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline hydrochloride salt

[00305] Step A: Preparation of benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate: Benzyl 2,5-dihydro-1H-pyrrole-1-carboxylate (11.0 g, 54.1 mmol, commercially available from Aldrich) and 3-chlorobenzoperoxide (17.3 g, 70.4 mmol) were added to 150 mL of chloroform and heated to 46 °C for 20 hours. The mixture was cooled, dichloromethane was added, and the reaction was washed with a saturated solution of NaHCO₃ and Na₂S₂CO₃. The combined organic layers were dried over MgSO₄, filtered and concentrated to give 10.5 g (88% isolated yield) of the desired compound as an oil, which was used directly in the next step.

[00306] Step B: Preparation of (trans)-benzyl 3-fluoro-4-hydroxypyrrolidine-1-carboxylate: benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (10.5 g, 47.9 mmol) and pyridine-hydrogen fluoride (14.2 g, 144.0 mmol) were added to a Teflon bottle containing dichloromethane and stirred vigorously overnight. After 20 hours, the reaction was slowly and carefully quenched with excess saturated solution of NaHCO₃ over several minutes and allowed to stir for one hour, and then the organic layer was isolated and washed with NaHCO₃ and a solution of brine. The combined organic layers were dried over MgSO₄, filtered and evaporated to yield an oil. This crude oil was purified on silica gel using ethyl acetate-hexane to produce 2.0 g (17% isolated yield) of the desired product as an oil.

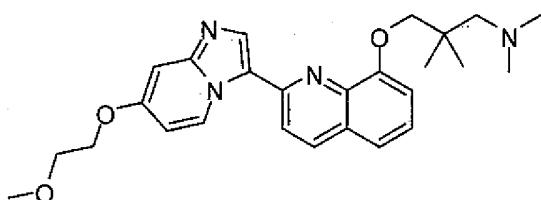
[00307] Step C: Preparation of (trans)-benzyl 3-fluoro-4-(methylsulfonyloxy)pyrrolidine-1-carboxylate: (trans)-Benzyl 3-fluoro-4-hydroxypyrrolidine-1-carboxylate (2.0 g, 8.36 mmol) was added to dichloromethane and cooled to 0 °C. Methanesulfonyl chloride (1.30 mL, 16.7 mmol) and triethylamine (2.3 mL, 16.7 mmol) were sequentially added, and the reaction was allowed to warm to ambient temperature overnight under vigorous stirring. The following day, additional dichloromethane was added, and the reaction mixture was washed with a saturated solution of NaHCO₃. The combined organic layers were dried over MgSO₄,

filtered and evaporated. The crude oil was purified on silica gel using ethyl acetate and hexane to produce 2.0 g (70% isolated yield) of the desired product as an oil.

[00308] Step D: Preparation of (cis)-benzyl 3-fluoro-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-1-carboxylate: 2-(7-(2-Methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (1.75 g, 5.22 mmol), (trans)-benzyl 3-fluoro-4-(methylsulfonyloxy)pyrrolidine-1-carboxylate (1.99 g, 6.3 mmol) and cesium carbonate (3.40 g, 10.4 mmol) were added to a sealed tube containing dimethylacetamide and heated to 100 °C overnight with stirring. The dimethylacetamide was removed under vacuum concentration and heat, chloroform was added, and this organic phase was gently washed with water. The combined organic layers were dried over MgSO₄, filtered and evaporated. The crude material was purified on silica gel using a 6% solution of ammonium hydroxide in methanol and dichloromethane to yield three major products which could not be separated further by column purification (starting quinoline phenol, product and unidentified by-product). MS APCI (+) m/z 557.3 (M+1) detected. This crude material was taken directly on to the deprotection step.

[00309] Step E: Preparation of 8-((cis)-4-fluoropyrrolidin-3-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline hydrochloride salt: Crude (cis)-benzyl 3-fluoro-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-1-carboxylate (1.0 g, 2.0 mmol) and palladium on carbon (1 g, 50% on a molar basis) were added to a mixture of ethanol and 1% HCl (v/v) and placed under hydrogen in a balloon with vigorous stirring. After 18 hours, the crude mixture was passed through Celite, rinsed several times with ethanol, and the collected filtrate was evaporated. The crude material was purified on silica gel using a 6% solution of ammonium hydroxide in methanol and dichloromethane to yield free base product, which, when subjected to HCl in dichloromethane and subsequent precipitation in diethyl ether yielded 150 mg (16% isolated yield) of highly pure product. MS APCI (+) m/z 423.3 (M+1) detected.

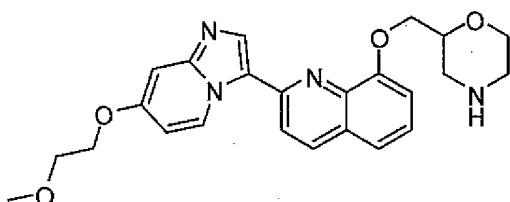
Example 15



3-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)-N,N,2,2-tetramethylpropan-1-amine

[00310] Prepared according to Example 3, substituting 3-(dimethylamino)-2,2-dimethylpropan-1-ol for tert-butyl 4-hydroxypiperidine-1-carboxylate (50 mg, 0.15 mmol)] MS ESI (+) m/z 449.2 (M+1) detected.

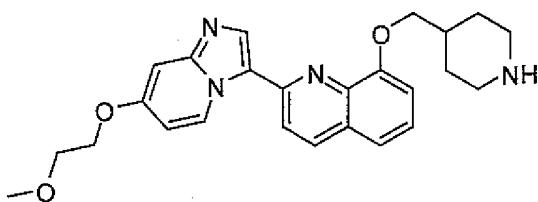
Example 16



2-((2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)methyl)morpholine

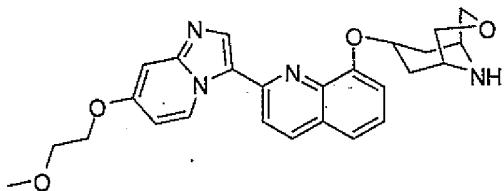
[00311] To a solution of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol [prepared as in Example 3; Step C; 50 mg, 0.15 mmol] in anhydrous DMA (2 mL) was added cesium carbonate (150 mg, 0.45 mmol) followed by tert-butyl 2-((methylsulfonyloxy)methyl)morpholine-4-carboxylate (130 mg, 0.45 mmol). The heterogeneous mixture was stirred at 100 °C for 16 hours and allowed to cool. The mixture was treated with water (20 mL) and extracted with EtOAc. The combined organic phases were washed with water and brine, then dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash column chromatography using gradient elution (CH₂Cl₂ to 1% MeOH/CH₂Cl₂ to 2% MeOH/CH₂Cl₂) to afford tert-butyl 2-((2-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)methyl)morpholine-4-carboxylate as a gum. This was dissolved in CH₂Cl₂ (4 mL) and treated with TFA (1 mL). After stirring for 2 hours at ambient temperature the mixture was concentrated. The residue was triturated with ether, filtered and dried in vacuo to provide 29.1 mg (76%) of desired product as its di-TFA salt as a powder. MS ESI (+) m/z 435.3 (M+1) detected.

Example 17



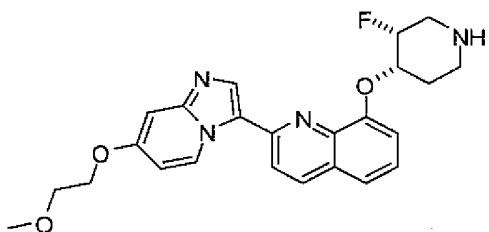
2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(piperidin-4-ylmethoxy)quinoline

[00312] Prepared according to the procedure for Example 16, using tert-butyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate in place of tert-butyl 2-((methylsulfonyloxy)methyl)morpholine-4-carboxylate. MS ESI (+) m/z 433.1 (M+1) detected.

Example 18

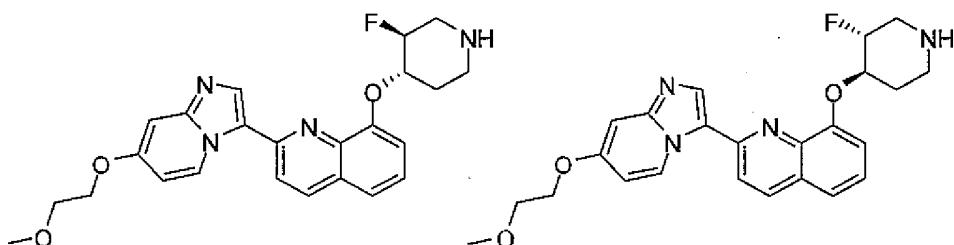
7-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)-3-oxa-9-azabicyclo[3.3.1]nonane

[00313] Prepared according to the procedure for Example 16, using tert-butyl 7-(methylsulfonyloxy)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate in place of tert-butyl 2-((methylsulfonyloxy)methyl)morpholine-4-carboxylate. MS APCI (+) m/z 461.2 (M+1) detected.

Example 19

8-((cis)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00314] Prepared according to the procedure for Example 16, using (trans)-tert-butyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate in place of tert-butyl 2-((methylsulfonyloxy)methyl)morpholine-4-carboxylate. MS ESI (+) m/z 437.2 (M+1) detected.

Example 20

8-((3S,4S)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline and 8-((3R,4R)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00315] Step A: Preparation of *tert*-butyl 4-(trimethylsilyloxy)-5,6-dihydropyridine-1(2H)-carboxylate: To a solution of *t*-butyl 4-oxopiperidine-1-carboxylate (52.6 g, 264 mmol) in anhydrous DMF (140 mL) was added TMSCl (40.2 mL, 317 mmol) followed by triethylamine (88.3 mL, 634 mmol). The resulting heterogeneous mixture was warmed to 80 °C and stirred for 16 hours. The cooled mixture was diluted with hexanes (500 mL), washed with saturated NaHCO₃ (3 x 300 mL) and brine (200 mL), then dried over Na₂SO₄, filtered and concentrated to afford 68 g (95%) of desired product as an oil.

[00316] Step B: Preparation of *tert*-butyl 3-fluoro-4-oxopiperidine-1-carboxylate: To a solution of *tert*-butyl 4-(trimethylsilyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (64.4 g, 237 mmol) in anhydrous ACN (1.5 L) at ambient temperature was added Selectfluor (92.5 g, 261 mmol) portionwise over 10 minutes, during which a slight exotherm (to 40 °C) was observed. The mixture was stirred for 2 hours, then concentrated to dryness and partitioned between EtOAc and brine. The aqueous layer was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated to afford 51 g (99%) of desired product as a solid.

[00317] Step C: Preparation of 3-fluoropiperidin-4-one hydrochloride: To a hazy solution of *tert*-butyl 3-fluoro-4-oxopiperidine-1-carboxylate (52.66 g, 242 mmol) in EtOAc (1 L) was added 4M HCl/dioxane (303 mL, 1212 mmol). The mixture was allowed to stir at ambient temperature for 16 hours. The resulting precipitate was collected by filtration, washed with EtOAc and dried *in vacuo* to afford 37 g (99%) of desired product as a solid.

[00318] Step D: Preparation of naphthalen-2-ylmethyl 3-fluoro-4-oxopiperidine-1-carboxylate: To a suspension of 3-fluoropiperidin-4-one hydrochloride (35.66 g, 232.2 mmol) in THF (800 mL) at 0 °C was added a solution of NaHCO₃ (46.81 g, 557.3 mmol) in water (800 mL). After most of the bubbling had subsided the ensuing solution was treated with a solution of naphthalen-2-ylmethyl carbonochloridate (56.36 g, 255.4 mmol) in THF (300 mL) dropwise, over 30 minutes. The mixture was allowed to warm to ambient temperature over 16 hours with vigorous stirring. The mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, then dried over Na₂SO₄, filtered and concentrated. The residue was triturated with methanol and the resulting solid was filtered and dried *in vacuo* to afford 41.8 g (60%) of desired product as a cream-colored powder.

[00319] Step E: Preparation of (*cis*)-naphthalen-2-ylmethyl 3-fluoro-4-hydroxypiperidine-1-carboxylate: To a suspension of naphthalen-2-ylmethyl 3-fluoro-4-

oxopiperidine-1-carboxylate (41.75 g, 138.6 mmol) in anhydrous THF (800 mL) at 0 °C was added L-Selectride (346 mL, 1.0 M, 346 mmol) dropwise over 30 minutes, during which a yellow solution formed. The solution was allowed to warm to ambient temperature and stir for 16 hours. The mixture was cooled to 0 °C, then treated with methanol (160 mL) and 2 N NaOH (350 mL) followed by the dropwise addition of 30% H₂O₂ (160 mL), during which an exotherm was observed. After stirring at 0 °C for an additional 1 hour and then at ambient temperature for 3 hours, the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified on a large silica gel plug eluting with hexanes:EtOAc, 1:1 to afford 26.78 g (64%) of desired product as a solid.

[00320] A 2 g sample of the material of Step E was separated by chiral HPLC (3 cm x 250 mm Chiral Technologies IA column; mobile phase 15% Ethanol, 85% hexanes; flow rate 28 mL/min; 50 mg/mL injections; 254 and 220 nM) to afford first eluting peak (Peak 1, 616 mg, Rt 17.70 min) in >99% ee and second eluting peak (Peak 2, 639 mg, Rt 22.12 min) in >99% ee, both as white solids. The material obtained from peak 1 was arbitrarily assigned as (3S,4R)-naphthalen-2-ylmethyl 3-fluoro-4-hydroxypiperidine-1-carboxylate. The material obtained from peak 2 was arbitrarily assigned as (3R,4S)-naphthalen-2-ylmethyl 3-fluoro-4-hydroxypiperidine-1-carboxylate.

[00321] Step F: Preparation of (3S,4R)-naphthalen-2-ylmethyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate and (3R,4S)-naphthalen-2-ylmethyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate: To a solution of naphthalen-2-ylmethyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (Peak 1), (616 mg, 2.03 mmol) in anhydrous CH₂Cl₂ (30 mL) at 0 °C was added triethylamine (368 μL, 2.64 mmol) followed by mesyl chloride (173 μL, 2.23 mmol). The mixture was allowed to warm slowly to ambient temperature over 16 hours, then treated with Et₃N (200 μL) and mesyl chloride (100 μL) and stirred for an additional 1 hour. The mixture was partitioned between CH₂Cl₂ (30 mL) and saturated NaHCO₃ (30 mL) and the aqueous layer was extracted with CH₂Cl₂. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash column chromatography (hexanes:EtOAc, 2:1) to afford 540 mg (70%) of desired product as a solid.

[00322] The compound of step E designated as Peak 2 (639 mg, 2.11 mmol) was treated in the same way to afford 616 mg (77%) of desired product as a white solid.

[00323] Step G: Preparation of (3S,4S)-naphthalen-2-ylmethyl 3-fluoro-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate and (3R,4R)-naphthalen-2-ylmethyl 3-fluoro-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: To a solution of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (prepared as in Example 3, 390 mg, 1.16 mmol) in anhydrous DMF (5 mL) was added cesium carbonate (1.14 g, 3.49 mmol) followed by naphthalen-2-ylmethyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate (Peak 1) (532 mg, 1.40 mmol). The heterogeneous mixture was warmed to 90 °C and stirred for 6 hours. The cooled mixture was treated with water (50 mL) and extracted with EtOAc. The combined organic phases were washed with water and brine, then dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash column chromatography using gradient elution (CH₂Cl₂ to 2% MeOH/CH₂Cl₂) to afford 293 mg (41%) of the Peak 1 desired product as a glass. MS APCI (+) m/z 621.2 (M+1) detected.

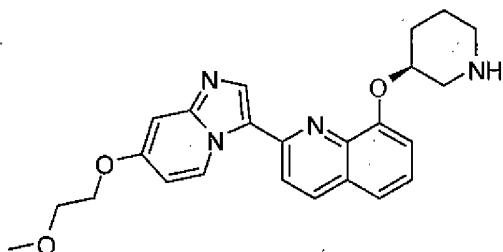
[00324] The (Peak 2) naphthalen-2-ylmethyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate (450 mg, 1.34 mmol) was treated in the same way to afford 325 mg (39%) of the Peak 2 desired product as a pale yellow glass. MS APCI (+) m/z 621.2 (M+1) detected.

[00325] Step H: Preparation of 8-((3S,4S)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline and 8-((3R,4R)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline: To a solution of the (Peak 1) naphthalen-2-ylmethyl 3-fluoro-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (293 mg, 0.47 mmol) in a 1:1 mixture of EtOH:EtOAc (20 mL) was added 10% Pd/C (wet, Degussa type, 30 mg). The mixture was purged with argon then allowed to stir under a balloon of H₂ for 16 hours. The mixture was treated with a further 20 mg of catalyst, recharged and hydrogenated for a further 16 hours. The mixture was filtered through GF paper and concentrated *in vacuo*. The residue was purified via flash column chromatography using gradient elution (CH₂Cl₂ to 2% MeOH/CH₂Cl₂ to 5% MeOH/CH₂Cl₂) to afford 128 mg (62%) of desired product as a solid. MS APCI (+) m/z 437.2 (M+1) detected.

[00326] The (Peak 2) naphthalen-2-ylmethyl 3-fluoro-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (325 mg, 0.52 mmol) was treated in the same way to afford 128 mg (56%) of desired product as a pale yellow solid. MS APCI (+) m/z 437.2 (M+1) detected. Chiral HPLC analysis confirmed

that the ee's were maintained and the elution order for final peaks was consistent with those of the alcohols from Step E.

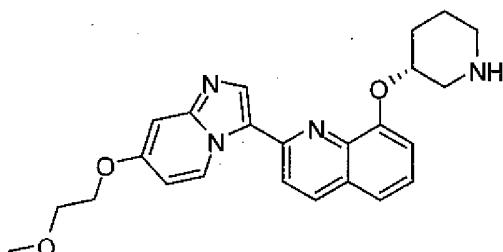
Example 21



(S)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(piperidin-3-yloxy)quinoline

[00327] Prepared according to the procedure for Example 16, using (R)-tert-butyl 3-(methylsulfonyloxy)piperidine-1-carboxylate in place of tert-butyl 2-((methylsulfonyloxy)methyl)morpholine-4-carboxylate. MS ESI (+) m/z 419.1 (M+1) detected.

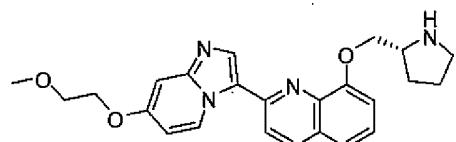
Example 22



(R)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(piperidin-3-yloxy)quinoline

[00328] Prepared according to the procedure for Example 16, using (S)-tert-butyl 3-(methylsulfonyloxy)piperidine-1-carboxylate in place of tert-butyl 2-((methylsulfonyloxy)methyl)morpholine-4-carboxylate. MS ESI (+) m/z 419.1 (M+1) detected.

Example 23

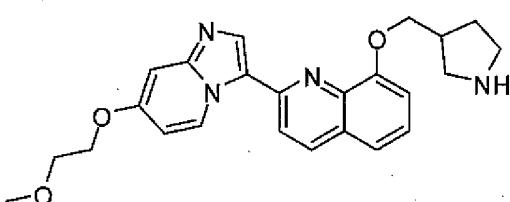


(R)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(pyrrolidin-2-ylmethoxy)quinoline

[00329] Step A: Preparation of (R)-tert-butyl 2-((2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)methyl)pyrrolidine-1-carboxylate: Prepared according to the procedure for Example 14 Step D, substituting (R)-tert-butyl 2-(tosyloxymethyl)pyrrolidine-1-carboxylate for (trans)-benzyl 3-fluoro-4-(methylsulfonyloxy)pyrrolidine-1-carboxylate.

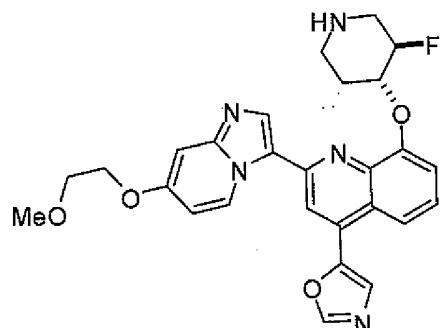
[00330] Step B: Preparation of (R)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(pyrrolidin-2-ylmethoxy)quinoline: (R)-tert-butyl 2-((2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)methyl)pyrrolidine-1-carboxylate (241 mg, 0.47 mmol) was dissolved in 10 mL of chloroform, followed by addition of 4.0M HCl in dioxane (4.65 ml, 9.3 mmol). The reaction was allowed to stir for 30 hours at ambient temperature at which time all starting material was consumed by LC/TLC. The reaction was concentrated in vacuo, followed by flash column chromatography (eluting with a 1-20% MeOH/DCM gradient), affording an oil on concentration. The crude oil was treated with 1000 uL of 4.0 M HCl in dioxane, affording the desired product (80 mg, 41 % yield). MS APCI (+) m/z 419.1 (M+1) detected.

Example 24



2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(pyrrolidin-3-ylmethoxy)quinoline

[00331] To a solution of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol [prepared as in Example 16; 204 mg, 0.61 mmol] in anhydrous DMA (5 mL) was added cesium carbonate (0.60 g, 1.8 mmol) followed by tert-butyl 3-((methylsulfonyloxy)methyl)pyrrolidine-1-carboxylate (221 mg, 0.79 mmol). The heterogeneous mixture was stirred at 70 °C for 20 hours and allowed to cool. The mixture was treated with water (50 mL) and extracted with chloroform and EtOAc. The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated to afford the crude product (386 mg, 122% yield) as a viscous oil. MS ESI (+) m/z 519.1 (M+1) detected. The oil (315 mg) was dissolved in CH₂Cl₂ (2 mL) and treated with TFA (1 mL). After stirring for 2 hours at ambient temperature the mixture was concentrated. The residue was treated with excess (20 ml) saturated aqueous sodium bicarbonate solution, and the resulting mixture was extracted with chloroform and EtOAc. The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated to afford a viscous oil. The oil was purified by column chromatography on silica gel (elution with 7 N NH₃/MeOH-chloroform) to provide the title compound (74 mg, 36% yield over two steps) as a solid. MS ESI (+) m/z 419.3 (M+1) detected.

Example 25

5-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-4-yl)oxazole

[00332] 1. Preparation of tert-butyl 2-ethynyl-6-methoxyphenylcarbamate

[00333] Step 1A: Preparation of tert-butyl 2-iodo-6-methoxyphenylcarbamate: To tert-butyl 2-methoxyphenylcarbamate (24.1 g, 108 mmol) in dry Et₂O (100 mL) at -20 °C was added dropwise tert-butyllithium (140 ml, 237 mmol). The clear solution turned cloudy at the end of the addition. The reaction was stirred for 3 hours at -20 °C, then cooled to -100 °C with a liquid N₂/Et₂O bath. Iodine (27.4 g, 108 mmol) in Et₂O (250 mL) was added to the solution. Following addition of I₂, the reaction was slowly warmed to ambient temperature over night. Na₂S₂O₃ (saturated, 200 mL) was then added to the reaction mix and phases were separated. The aqueous was extracted with Et₂O, and the combined organic layers were dried (MgSO₄), filtered and concentrated. DCM (50 mL) was added, followed by hexanes (200 mL). The solution was concentrated to remove DCM. The product crashed out, and was collected by filtration and washed with hexanes (100 mL) to give the crude product (58%).

[00334] Step 1B: Preparation of tert-butyl 2-methoxy-6-((trimethylsilyl)ethynyl)phenylcarbamate: To tert-butyl 2-iodo-6-methoxyphenylcarbamate (10.36 g, 29.67 mmol), ethynyltrimethylsilane (3.20 g, 32.63 mmol), copper(I) iodide (0.28 g, 1.48 mmol), and PdCl₂(PPh₃)₂ (1.04 g, 1.48 mmol) in THF (100 mL) was added triethylamine (3.60 g, 35.6 mmol), followed by overnight stirring. The crude reaction was then concentrated and the mixture was flashed through silica gel with 10:1 Hex/EtOAc to give the desired product (98%).

[00335] Step 1C: Preparation of tert-butyl 2-ethynyl-6-methoxyphenylcarbamate: To tert-butyl 2-methoxy-6-((trimethylsilyl)ethynyl)phenylcarbamate (4.21 g, 13.2 mmol) in MeOH (30 mL) was added K₂CO₃ (9.11 g, 65.9 mmol). The reaction was stirred for 30 minutes, then filtered and washed with DCM (50 mL). The combined organic layers were concentrated and diluted with DCM (20 mL), filtered, washed a second time with DCM (50 mL), then

concentrated. The residue was purified by flash chromatography through a pad of silica gel with 10:1 Hexane/EtOAc (500 mL), affording the desired product (62%).

[00336] 2. Preparation of N-methoxy-7-(2-methoxyethoxy)-N-methylimidazo[1,2-a]pyridine-3-carboxamide

[00337] Step 2A: Preparation of ethyl 7-(2-methoxyethoxy)imidazo[1,2-a]pyridine-3-carboxylate: Ethyl 2-chloro-3-oxopropanoate (5.1 g, 33.9 mmol, Heterocycles 1991, pg. 699) and 4-(2-methoxyethoxy)pyridin-2-amine (5.70 g, 33.9 mmol) was dissolved in EtOH (50 mL) and heated to reflux overnight. The crude reaction mixture was concentrated and purified by flash column chromatography (EtOAc/MeOH 10:0 to 10:1) provided the desired product (57%).

[00338] Step 2B: Preparation of 7-(2-methoxyethoxy)imidazo[1,2-a]pyridine-3-carboxylic acid: To ethyl 7-(2-methoxyethoxy)imidazo[1,2-a]pyridine-3-carboxylate (5.01 g, 19.0 mmol) in THF/EtOH (32/6 mL) was added lithium hydroxide (37.9 ml, 37.9 mmol), and the reaction was stirred overnight. HCl (57 mmol, 2M in ether) was added to the mixture, followed by concentration to give the desired product.

[00339] Step 2C: Preparation of N-methoxy-7-(2-methoxyethoxy)-N-methylimidazo[1,2-a]pyridine-3-carboxamide: To EDCI (2.196 g, 11.45 mmol) and HOBT-H₂O (1.754 g, 11.45 mmol) in DMF (50 mL) was added N-ethyl-N-isopropylpropan-2-amine (1.480 g, 11.45 mmol), followed by the addition of N,O-dimethylhydroxylamine hydrochloride (1.117 g, 11.45 mmol). The reaction was stirred overnight, followed by concentration to remove most of the DMF. The crude mixture was diluted with saturated NaHCO₃ (20 mL)/EtOAc (40 mL). The aqueous phase was ten extracted with EtOAc, dried over Na₂SO₄ and concentrate to give the desired product (72%).

[00340] 3. Preparation of 5-(8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-4-yl)oxazole

[00341] Step 3A: Preparation of tert-butyl 2-methoxy-6-(3-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-3-oxoprop-1-ynyl)phenylcarbamate: To tert-butyl 2-ethynyl-6-methoxyphenylcarbamate (1.77 g, 7.18 mmol) in THF (40 mL) was added butyllithium (0.919 g, 14.4 mmol) at -78 °C, and the reaction was stirred for 1 hour. N-methoxy-7-(2-methoxyethoxy)-N-methylimidazo[1,2-a]pyridine-3-carboxamide (1.67 g, 5.98 mmol) in THF (55 mL) was then added to the reaction mixture dropwise. After the addition, the cold bath was removed and the reaction was warmed to ambient temperature. Following a 2 hour stir at

ambient temperature, the reaction mixture was poured into cold saturated NH₄Cl (40 mL) and EtOAc (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc, dried over Na₂SO₄, filtered and concentrated. The residue was triturated with DCM to give product as a solid. The DCM solution was concentrated and purified by flash column chromatography (EtOAc/MeOH 10:0 to 10:1) to provide the desired product.

[00342] Step 3B: Preparation of 4-iodo-8-methoxy-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline: To tert-butyl 2-methoxy-6-(3-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-3-oxoprop-1-ynyl)phenylcarbamate (2.51 g, 5.39 mmol) and sodium iodide (16.2 g, 108 mmol) was added acetic acid/formic acid (5 mL/5 mL). The reaction vessel was purged with N₂ and heated to 60 °C for 3 hours. The reaction was then cooled to ambient temperature and diluted with H₂O/DCM (50 mL/100 mL), followed by extraction with DCM. The combined organics were washed with saturated NaHCO₃, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/MeOH 10:1) provided the desired product (92%).

[00343] Step 3C: Preparation of 8-methoxy-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-4-vinylquinoline: To 4-iodo-8-methoxy-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline (898 mg, 1.89 mmol) in NMP (10 mL) was added Pd₂dba₃ (87 mg, 0.09 mmol), trifuran-2-ylphosphine (88 mg, 0.37 mmol) and tributyl(vinyl)stannane (659 mg, 2.1 mmol). The reaction flask was purged with N₂ and the reaction was stirred at 80 °C for 2 hours. The crude mixture was diluted with EtOAc (30 mL) then washed with H₂O, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (EtOAc/Hexane 8:1) affording the desired product (80%).

[00344] Step 3D: Preparation of 1-(8-methoxy-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-4-yl)ethane-1,2-diol: To 8-methoxy-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-4-vinylquinoline (656 mg, 1.75 mmol) in DCM (20 mL) at 0 °C was added dropwise a solution of triethylbenzylammonium chloride (504 mg, 2.62 mmol) and KMnO₄ (414 mg, 2.62 mmol) in DCM (40 mL), and the reaction was stirred for 2 hours at 0 °C. The reaction mixture was then warmed to ambient temperature and treated with 3% NaOH (30 mL). The mixture was filtered through celite and washed with DCM (100 mL), followed by extraction with DCM. The combined organic phases were dried over Na₂SO₄, filtered and concentrated to give the desired product (44%).

[00345] Step 3E: Preparation of 8-methoxy-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline-4-carbaldehyde: To silica gel (1.5 g) in DCM (5 mL) was added dropwise sodium periodate (131 μ L, 0.850 mmol), affording a slurry after the addition. 1-(8-Methoxy-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-4-yl)ethane-1,2-diol (232 mg, 0.567 mmol) in DCM (3 mL) was added to the slurry, followed by 30 minute stir. The mixture was then filtered, washed with DCM (10 mL), and concentrated to give the desired product (100%).

[00346] Step 3F: Preparation of 5-(8-methoxy-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-4-yl)oxazole: To 8-Methoxy-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline-4-carbaldehyde (210 mg, 0.556 mmol) and 1-(isocyanomethylsulfonyl)-4-methylbenzene (130 mg, 0.668 mmol) in MeOH (5 mL) was added K_2CO_3 (154 mg, 1.11 mmol), followed by heating to reflux for 3 hours. The reaction was then cooled to ambient temperature, concentrated and purified by flash column chromatography (EtOAc/MeOH 10:1) providing the desired product (73%). MS APCI (+) m/z 417.2 (M+1) detected.

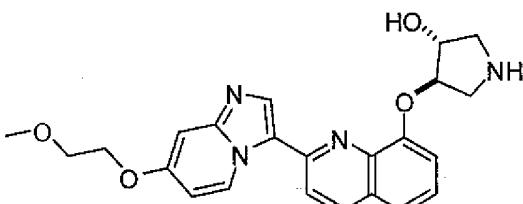
[00347] Step 3G: Preparation of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-4-(oxazol-5-yl)quinolin-8-ol: To 5-(8-methoxy-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-4-yl)oxazole (80 mg, 0.19 mmol) in DMF (3 mL) was added sodium ethanethiolate (162 mg, 1.9 mmol). The reaction vial was sealed and heated to 150 °C for 2 hours. The reaction was then cooled to ambient temperature and concentrated. The residue was purified by flash column chromatography (DCM/MeOH 10:1) providing the desired product (39%).

[00348] Step 3H: Preparation of (trans)-tert-butyl 3-fluoro-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-4-(oxazol-5-yl)quinolin-8-yloxy)piperidine-1-carboxylate: To 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-4-(oxazol-5-yl)quinolin-8-ol (9 mg, 0.02 mmol) in DMA (2 mL) was added (cis)-tert-butyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate (13 mg, 0.04 mmol) and Cs_2CO_3 (22 mg, 0.07 mmol). The reaction vial was sealed and heated to 106 °C for 4 hours. The reaction was cooled to ambient temperature and concentrated. The crude residue was purified by flash column chromatography (DCM/MeOH 10:1) providing the desired product (3 %).

[00349] Step 3I: Preparation of 5-(8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-4-yl)oxazole: To (trans)-tert-butyl 3-fluoro-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-4-(oxazol-5-yl)quinolin-8-yloxy)

piperidine-1-carboxylate (4 mg, 0.007 mmol) in DCM (1 mL) was added TFA (1 mL), followed by a 30 minute stir. The crude reaction was concentrated and purified by flash column chromatography (DCM/MeOH/NH₄OH 10:1:0.1) affording the desired product (60%). MS APCI (+) m/z 504.2 (M+1) detected.

Example 26



(trans)-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidin-3-ol

[00350] 1. Preparation of naphthalen-2-ylmethyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate:

[00351] Step 1A: Preparation of naphthalen-2-ylmethyl 2,5-dihydro-1H-pyrrole-1-carboxylate: Naphthalen-2-ylmethyl carbonochloride (31.93 g, 144.7 mmol) was added to a solution of 2,5-dihydro-1H-pyrrole (10 g, 144.7 mmol) in a 1:1 mixture of saturated NaHCO₃ (400 mL) and THF (400 mL). The reaction was stirred for 12 hours, condensed to a small volume, diluted with saturated NaHCO₃, extracted with CH₂Cl₂, wash with 1 N HCl, dried over sodium sulfate, filtered and condensed to afford 27.5 g of the desired product as a solid.

[00352] Step 1B: Preparation of naphthalen-2-ylmethyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate: mCPBA (4.203 g, 17.04 mmol) was added to a solution of naphthalen-2-ylmethyl 2,5-dihydro-1H-pyrrole-1-carboxylate (2.15 g, 8.52 mmol) in chloroform (35 mL), and the reaction was stirred for 4 days. The reaction mixture was diluted with saturated NaHCO₃ and chloroform, and the organic layer was washed with CHCl₃, dried over sodium sulfate and condensed. The residue was purified by silica gel chromatography, eluting with a gradient from 1% EtOAc/DCM to 15 % EtOAc/DCM, to provide the desired product as a solid (1.0 g).

[00353] 2. Preparation of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol

[00354] Step 2A: Preparation of 8-(benzyloxy)quinolin-2-ol: To a flask was added quinoline-2,8-diol (20.0 g, 124.1 mmol), K₂CO₃ (17.15 g, 124.1 mmol), benzyl bromide (14.76 ml, 124.1 mmol) and DMF (124.1 ml, 124.1 mmol). The resulting mixture was heated to 65 °C overnight. The reaction mixture was poured into 1000 ml water and stirred for 5 hours, filtered

solids and then washed with 1000 ml diethyl ether to yield 26.5 g (85 % yield) of desired product.

[00355] Step 2B: Preparation 8-(benzyloxy)-2-chloroquinoline: A flask was charged with 8-(benzyloxy)quinolin-2-ol (26.5 g, 105 mmol) and DCE (105 ml, 105 mmol). Oxalyl chloride (18.4 ml, 211 mmol) was added dropwise, and then a couple of drops of DMF (0.5 ml, 105 mmol) were added. The reaction was heated to 85 °C overnight, then cooled to ambient temperature and concentrated to an oil. DCM (300 mL) was added to the oil, and the organic layer was washed with 300 ml of saturated NaHCO₃. The layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated to an oil. The oil was crystallized from toluene to yield 28.4 g of desired product (quantitative yield).

[00356] Step 2C: Preparation of 8-(benzyloxy)-2-(7-(2-methoxyethoxy)-imidazo[1,2-a]pyridin-3-yl)quinoline: 8-(BenzylOxy)-2-chloroquinoline (5.0 g, 18.5 mmol), 7-(2-methoxyethoxy)-imidazo[1,2-a]pyridine (3.56 g, 18.5 mmol), Pd(PPh₃)₄ (1.07 g, 0.927 mmol), K₂CO₃ (5.12 g, 37.1 mmol), and Pd(OAc)₂ (0.208 g, 0.927 mmol) were added into dioxane (74.1 ml, 18.5 mmol) and water (0.735 ml, 40.8 mmol) and heated to 100 °C overnight under nitrogen. The reaction was diluted with DCM and carbon (5 g) was added, followed by filtration. The filtrate was concentrated and then triturated with 1:1 EtOAc/MTBE (30 mL). The resulting solids were allowed to stir for 5 hours and then filtered to isolate of the desired product as a solid (5.4 g, 69% yield).

[00357] Step 2D: Preparation of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol: 8-(BenzylOxy)-2-(7-(2-methoxyethoxy)-imidazo[1,2-a]pyridin-3-yl)quinoline (5.00 g, 11.8 mmol) was slurried in MeOH (118 ml). Ammonium formate (7.41 g, 117 mmol) and Pd(OH)₂/C (0.82 g, 0.59 mmol) were added, and the reaction was heated at reflux for 2 hours. The reaction mixture was cooled to 20 °C and formic acid was added to the slurry until solids went into solution. The resulting mixture was filtered and washed with 100 ml 10 % formic acid in methanol. The filtrate was concentrated to an oil. To the oil was added an excess of NH₃ in methanol and resulting the solids were concentrated to dryness. Water was added and solids were allowed to stir for 1 hour (pH was 6.5-7.0 by pH paper). The solids were collected by filtration and then taken up in toluene and concentrated to dryness. The solids were dried under vacuum for 12 hours to obtain 3.8 g (96% yield) of the desired product.

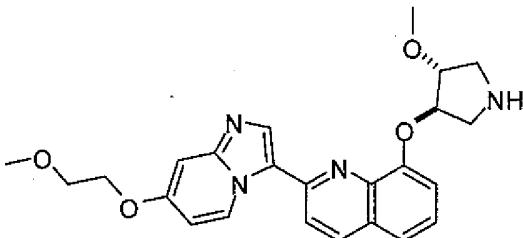
[00358] 3. Preparation of (trans)-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidin-3-ol

[00359] Step 3A: Preparation of (trans)-naphthalen-2-ylmethyl 3-hydroxy-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-1-carboxylate:

Cs_2CO_3 (0.2201 g, 1.141 mmol) was added to a solution of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (0.294 g, 0.878 mmol) and (cis)-naphthalen-2-ylmethyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.260 g, 0.966 mmol) in DMF (4.5 mL). The reaction was heated to 100 °C overnight, then cooled and poured into 30 mL of ice water. This mixture was extracted with 25 % IPA in CH_2Cl_2 , and the organic layer was dried over sodium sulfate and condensed. The residue was purified by silica gel chromatography, eluting with gradient from 1 % to 25 % MeOH (with 6% NH_4OH) in EtOAc, to collect 223 mg of the desired product. MS APCI (+) m/z 605.1 ($M+1$) detected.

[00360] Step 3B: Preparation of (trans)-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidin-3-ol: A 25 mL flask was charged with (trans)-naphthalen-2-ylmethyl 3-hydroxy-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-1-carboxylate (0.100 g, 0.165 mmol), EtOH (1.6 mL), THF (1.6 mL), 2 N HCl (0.2 mL) and 10 % Degussa type Pd/C (0.018 g, 0.017 mmol), and the reaction was placed under a balloon of H_2 and stirred for 2 hours. The reaction was filtered (GF/F paper), the filter paper was washed with 2 N HCl and THF, the aqueous phase was washed with DCM, neutralized with saturated NaHCO_3 , and then extracted with DCM. The organic layer was dried and condensed to afford 14 mg of the desired product. MS APCI (+) m/z 421.2 ($M+1$) detected.

Example 27



2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-((trans)-4-methoxypyrrolidin-3-yloxy)quinoline

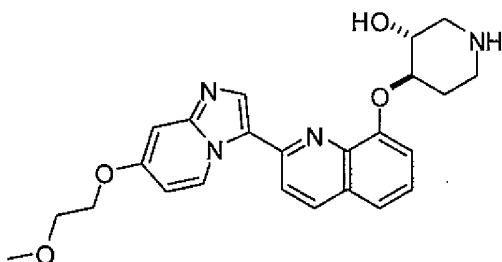
[00361] Step A: Preparation of (trans)-naphthalen-2-ylmethyl 3-methoxy-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-1-carboxylate.

Sodium hydride (0.017 g, 0.43 mmol) was added to a solution of (trans)-naphthalen-2-ylmethyl 3-hydroxy-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-1-carboxylate (0.117 g, 0.194 mmol) in DMF (1 mL). The reaction was cooled to 0 °C and

stirred for 20 minutes. Iodomethane (0.012 ml, 0.194 mmol) was added, and the ice bath was removed. The reaction was stirred for 1 hour. Water was added, and the reaction mixture was extracted with CHCl₃. The combined organic layers were washed with brine, dried and condensed. The residue was purified by silica gel chromatography to provide 54 mg of the desired product. MS APCI (+) m/z 619.1 (M+1) detected.

[00362] Step B: Preparation of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-((trans)-4-methoxypyrrolidin-3-yloxy)quinoline: A flask was charged with (trans)-naphthalen-2-ylmethyl 3-methoxy-4-(2-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-1-carboxylate (0.054 g, 0.087 mmol), 2 N HCl (0.1 mL), THF (1 mL), EtOH (1 mL), and 10% Degussa type Pd/C (0.0186 g, 0.0175 mmol), and the reaction mixture was placed under a balloon of H₂ and stirred for 3 hours. The reaction was neutralized with saturated NaHCO₃ and filtered (GF/F paper). The filter cake was washed with CHCl₃ and water. The layers were separated, the aqueous phase was washed with chloroform, and the organic phase was dried over Na₂SO₄, filtered and condensed. The residue was purified by silica gel chromatography to provide 24 mg of the desired product. MS APCI (+) m/z 435.2 (M+1) detected.

Example 28



(trans)-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidin-3-ol

[00363] Step A: Preparation of naphthalen-2-ylmethyl carbonochloride: A solution of naphthalen-2-yl methanol (51.2 g, 324 mmol) dissolved in anhydrous THF (1 L) was treated with phosgene (205 mL, 20 % solution in toluene, 388 mmol). The solution was stirred at ambient temperature for 45 minutes and then concentrated to afford the desired product as a solid, which was dried under vacuum and used directly in the next step.

[00364] Step B: Preparation of naphthalen-2-ylmethyl 5,6-dihydropyridine-1(2H)-carboxylate: Naphthalen-2-ylmethyl carbonochloride (11.00 g, 49.85 mmol) was dissolved in THF (25 mL) and this was added dropwise to a cooled (0 °C) solution of 1,2,3,6-tetrahydropyridine (3.79 mL, 41.5 mmol) and NaHCO₃ (4.18 g, 49.8 mmol) in water (88 mL). A

precipitate formed in the reaction immediately, therefore after the addition, additional THF (63 mL) was added to solubilize the reaction mixture. The solution was removed from the bath and warmed to ambient temperature for 16 hours. The reaction was concentrated in vacuo then methylene chloride was added. The mixture was separated, the aqueous layer was washed with methylene chloride, and the combined organics were dried over Na₂SO₄ and concentrated in vacuo to provide the desired product as an oil (11 g).

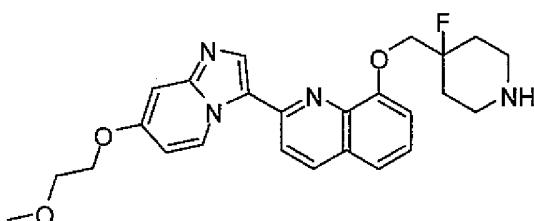
[00365] Step C: Preparation of naphthalen-2-ylmethyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate: A suspension of mCPBA (13.02 g, 58.13 mmol) dissolved in methylene chloride (50 mL) was added dropwise to a cooled (0 °C) solution of naphthalen-2-ylmethyl 5,6-dihydropyridine-1(2H)-carboxylate (11 g, 41.5 mmol) dissolved in methylene chloride (33 mL). The solution was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with 5% K₂CO₃ and then the layers were separated. The organic phase was washed with 5% K₂CO₃, saturated NaCl, dried over Na₂SO₄ and concentrated in vacuo (9.5 g).

[00366] Step D: Preparation of (trans)-naphthalen-2-ylmethyl 3-hydroxy-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: 2-(7-(2-Methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (0.10 g, 0.309 mmol) was slurried in DMA (1.0 mL) and treated with Cs₂CO₃ (0.201 g, 0.618 mmol). After 10 minutes, naphthalen-2-ylmethyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (0.100 g, 0.355 mmol) was added. The reaction was warmed to 90°C and stirred for 40 hours. The reaction mixture was cooled to ambient temperature then added dropwise into saturated NH₄Cl (5 mL). Chloroform (25 mL) was added and the layers were separated. The aqueous layer was washed with CHCl₃ and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with a gradient from 1 to 20% (6% NH₄OH in MeOH)/ethyl acetate to provide the desired product (111 mg). MS ESI (+) m/z 619.2 (M+1) detected.

[00367] Step E: Preparation of (trans)-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidin-3-ol: (trans)-Naphthalen-2-ylmethyl 3-hydroxy-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (0.045 g, 0.072 mmol) was dissolved in 95 % EtOH/ethyl acetate (1:1, 2 mL) and treated with 10% Pd/C (Degeussa type, 20 mg). The reaction was purged with argon then subjected to hydrogen atmosphere at balloon pressure. After 19 hours, the reaction was purged with N₂ and treated

with fresh catalyst (ca. 5 mg) and re-subjected to hydrogen atmosphere for 5 hours. The reaction was filtered through a nylon membrane (0.45 μ M) and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with a gradient from 1-20% (6% NH₄OH in MeOH)/ethyl acetate. A solid was recovered after concentration in vacuo. The solid was dissolved in MeOH (2 mL) and treated with 4 M HCl in dioxane (0.5 mL). After stirring for 10 minutes the solution was concentrated in vacuo, then re-dissolved in MeOH and re-concentrated three times. The material was dissolved in MeOH (1 mL) then added dropwise to Et₂O (40 mL). A precipitate formed, and after stirring for 20 minutes, this precipitate was collected by filtration, washed with Et₂O and dried under a blanket of nitrogen (15 mg). ¹H NMR (400 MHz, CD₃OD) δ 10.72 (d, 1H), 8.75 (s, 1H), 8.45 (d, 1H), 8.11 (d, 1H), 7.65-7.59 (m, 2H), 7.49-7.43 (m, 1H), 7.43-7.38 (m, 2H), 4.94-4.87 (m, 1H), 4.48-4.43 (m, 2H), 4.37-4.32 (m, 1H), 3.89-3.84 (m, 2H), 3.64-3.57 (m, 1H), 3.49-3.40 (m, 1H), 3.46 (s, 3H), 3.37-3.31 (m, 1H), 2.58-2.48 (m, 1H), 2.27-2.18 (m, 1H). MS APCI (+) m/z 435.1 (M+1) detected.

Example 29



8-((4-fluoropiperidin-4-yl)methoxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00368] Step A: Preparation of tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate: 4-Fluoro-1-(1,1-dimethylethyl)1,4-piperidinedicarboxylic acid-4-ethyl ester (0.40 g, 1.45 mmol) was dissolved in THF (1.5 mL), cooled to 0 °C and treated with lithium aluminum hydride (1 M in THF, 2.90 ml, 2.90 mmol). The reaction mixture was stirred at 0 °C for 2 hours, then warmed to ambient temperature for 3 hours. The reaction was quenched with sequential additions of water (110 μ L), 15% NaOH (110 μ L), and water (330 μ L), and then stirred for 20 minutes. The slurry was diluted with ethyl acetate and filtered. The filtrate was concentrated in vacuo to provide the desired product (0.303 g).

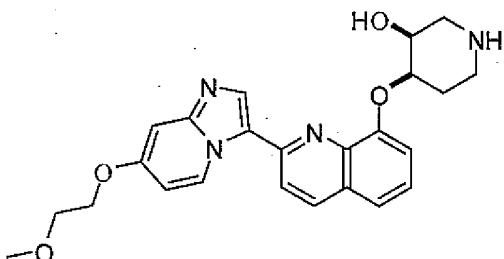
[00369] Step B: Preparation of tert-butyl 4-fluoro-4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate: tert-Butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (0.150 g, 0.643 mmol) was dissolved in dichloromethane (1.8 mL) and cooled to 0 °C. The solution was treated with triethylamine (0.134 ml, 0.964 mmol) followed by

methanesulfonyl chloride (0.0547 ml, 0.707 mmol). The reaction was stirred at 0 °C for 2 hours then diluted with methylene chloride and quenched with saturated NH₄Cl and separated. The organic layer was washed with saturated NH₄Cl, 6% NaHCO₃, dried over Na₂SO₄, filtered and concentrated in vacuo to provide the desired product (200 mg).

[00370] Step C: Preparation of tert-butyl 4-fluoro-4-((2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)methyl)piperidine-1-carboxylate: 2-(7-(2-Methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (0.050 g, 0.149 mmol) was dissolved in DMA (0.5 mL) and treated with Cs₂CO₃ (0.097 g, 0.29 mmol). After stirring for several minutes, tert-butyl 4-fluoro-4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate (0.053 g, 0.171 mmol) was added. The mixture was heated to 90 °C for 40 hours. The entire reaction mixture was applied to a SiO₂ column and eluted with a gradient from 1-20 % (6 % NH₄OH in MeOH)/ethyl acetate to provide the desired product (11 mg). MS ESI (+) m/z 551.1 (M+1) detected.

[00371] Step D: Preparation of 8-((4-fluoropiperidin-4-yl)methoxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline: tert-Butyl 4-fluoro-4-((2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)methyl)piperidine-1-carboxylate (0.011 g, 0.020 mmol) was dissolved in dioxane (0.5 mL) and treated with 4 M hydrogen chloride in dioxane (0.126 ml, 0.504 mmol). The reaction was stirred at ambient temperature for 24 hours. The mixture was concentrated in vacuo, redissolved and re-concentrated from MeOH three times. The crude material was loaded onto a SiO₂ column and eluted with a gradient from 1 to 20% (6% NH₄OH in MeOH)/ethyl acetate to provide the desired product (3 mg). ¹H NMR (400 MHz, CDCl₃) δ 10.67 (d, 1H), 8.22 (s, 1H), 8.08 (d, 1H), 7.83 (s, 1H), 7.41-7.33 (m, 2H), 7.09-6.98 (m, 2H), 6.90-6.84 (m, 1H), 4.29-4.16 (m, 3H), 3.87-3.79 (m, 2H), 3.49 (s, 3H), 3.23-3.10 (m, 3H), 2.29-2.15 (m, 1H), 2.14-1.94 (m, 2H), 0.93-0.81 (m, 1H). MS APCI (+) m/z 451.2 (M+1) detected.

Example 30



(cis)-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidin-3-ol

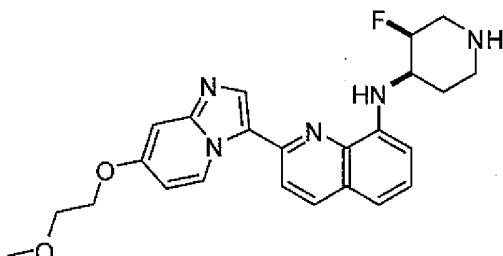
[00372] Step A: Preparation of (cis)-naphthalen-2-ylmethyl 3-(benzoyloxy)-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: (trans)-Naphthalen-2-ylmethyl 3-hydroxy-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (Example 28, Steps A-D; 0.075 g, 0.121 mmol) was dissolved in THF (0.50 mL) and treated with benzoic acid (0.022 g, 0.181 mmol), PPh₃ (0.036 g, 0.139 mmol) and diisopropylazodicarboxylate (0.026 ml, 0.133 mmol). The mixture was stirred at ambient temperature for 40 hours, and then the whole reaction mixture was applied to a column of SiO₂ and eluted with a gradient from 1-20% (6% NH₄OH in MeOH)/ethyl acetate (75 mg). MS ESI (+) m/z 723.2 (M+1) detected.

[00373] Step B: Preparation of (cis)-naphthalen-2-ylmethyl 3-hydroxy-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: (cis)-Naphthalen-2-ylmethyl-3-(benzoyloxy)-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (0.075 g, 0.103 mmol) was dissolved in THF/MeOH/water (2:2:1, 0.5 mL) and cooled to 0 °C. The solution was treated with LiOH-H₂O (0.008 g, 0.2 mmol) and stirred at ambient temperature for 5 days. The reaction was quenched with saturated NH₄Cl and concentrated in vacuo. The residue was diluted with CHCl₃ and separated. The aqueous layer (pH ca. 8) was extracted 3 additional times with CHCl₃. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The material was purified by silica gel chromatography, eluting with a gradient from 1-20% (6% NH₄OH in MeOH)/ethyl acetate to provide the desired product (31.2 mg). MS ESI (+) m/z 619.1 (M+1) detected.

[00374] Step C: Preparation of (cis)-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidin-3-ol: (cis)-Naphthalen-2-ylmethyl-3-hydroxy-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (0.030 g, 0.048 mmol) was dissolved in EtOH (1 mL), treated with 10% palladium on carbon (Degussa type, 50 mg), placed under a hydrogen atmosphere (balloon pressure) and stirred for 3 days. The reaction was filtered through a nylon membrane and concentrated in vacuo. The mixture was purified by preparative TLC (10 cm x 20 cm x 0.5 mm) eluting with 20% (6% NH₄OH in MeOH)/ethyl acetate. The recovered product was dissolved in MeOH and treated with 4 M HCl in dioxane then concentrated in vacuo. The residue was re-dissolved in MeOH and re-concentrated three times. The residue was slurried in MeOH (0.3 mL) and added

dropwise to Et₂O (20 mL). The resultant solid was filtered and dried under N₂ to provide the desired product (3 mg). MS ESI (+) m/z 435.1 (M+1) detected.

Example 31



N-((cis)-3-fluoropiperidin-4-yl)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-amine

[00375] 1. Preparation of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yl trifluoromethanesulfonate:

[00376] Step 1A: Preparation of 8-(benzyloxy)quinolin-2-ol: A flask was charged with quinoline-2,8-diol (20.0 g, 124.1 mmol), K₂CO₃ (17.15 g, 124.1 mmol), benzyl bromide (14.76 ml, 124.1 mmol) and DMF (124.1 ml, 124.1 mmol). The resulting mixture was heated to 65 °C overnight, then poured into 1000 ml water and stirred for 5 hours. The solids were filtered and washed with 1000 ml diethyl ether to yield 26.5 g (85% yield) of desired product.

[00377] Step 1B: Preparation 8-(benzyloxy)-2-chloroquinoline: A flask was charged with 8-(benzyloxy)quinolin-2-ol (26.5 g, 105 mmol) and DCE (105 ml, 105 mmol). Oxalyl chloride (18.4 ml, 211 mmol) was added dropwise, followed by a few drops of DMF (0.5 ml, 105 mmol), and the reaction mixture was heated to 85 °C overnight. The reaction was cooled to ambient temperature and concentrated to an oil. DCM (300 mL) was added to the oil and the organic layer was washed with 300 ml of saturated NaHCO₃. The layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated to an oil. The oil was crystallized from toluene to yield 28.4 g of desired product (quantitative yield).

[00378] Step 1C: Preparation of 8-(benzyloxy)-2-(7-(2-methoxyethoxy)-imidazo[1,2-a]pyridin-3-yl)quinoline: 8-(Benzyl)quinolin-2-ol (5.0 g, 18.5 mmol), 7-(2-methoxyethoxy)-imidazo[1,2-a]pyridine (3.56 g, 18.5 mmol), Pd(PPh₃)₄ (1.07 g, 0.927 mmol), K₂CO₃ (5.12 g, 37.1 mmol), and Pd(OAc)₂ (0.208 g, 0.927 mmol) were added to dioxane (74.1 ml, 18.5 mmol) and water (0.735 ml, 40.8 mmol) and the reaction mixture was heated to 100 °C overnight under nitrogen. The reaction was diluted with DCM and 5 g of carbon were added followed by filtration. The slurry was concentrated and the filtrate was triturated with 1:1

EtOAc/MTBE (30 mL). The resulting solids were stirred for 5 hours and then filtered to isolate the desired product as a solid (5.4 g, 69 % yield).

[00379] Step 1D: Preparation of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol: 8-(Benzylxy)-2-(7-(2-methoxyethoxy)-imidazo[1,2-a]pyridin-3-yl)quinoline (5.0 g, 11.75 mmol) was slurried in MeOH (117.5 ml). Ammonium formate (7.410 g, 117.5 mmol) and Pd(OH)₂/C (0.8252 g, 0.5876 mmol) were added. The reaction mixture was heated to reflux for 2 hours, then cooled to 20 °C. Formic acid was added to the slurry until solids went into solution. The mixture was filtered and the filter paper was washed with 10 % formic acid in methanol. The filtrate was concentrated to an oil. To the oil was added an excess of NH₃ in methanol and resulting the solids were concentrated to dryness. Water was added to the solids and the slurry was stirred for 1 hour (pH was 6.5-7.0 by pH paper). The solids were collected by filtration and then taken up in toluene and concentrated to dryness under vacuum dry for 12 hours to obtain 3.8 g (96 % yield) of the desired product.

[00380] 2. Preparation of N-((cis)-3-fluoropiperidin-4-yl)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-amine

[00381] Step 2A: Preparation of tert-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate: tert-Butyl 3-fluoro-4-oxopiperidine-1-carboxylate [van Niel, M.B.; et al.; J. Med. Chem. 1999, 42, 2087-2104] (52.27 g, 241 mmol) was dissolved in anhydrous MeOH (600 mL), cooled to 0 °C and treated in portions with sodium borohydride (37.8 g, 361 mmol) over a 15 minute period. After stirring at 0 °C for 30 minutes, the mixture was stirred at ambient temperature for 4 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between saturated ammonium chloride solution (400 mL) and EtOAc (400 mL). The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated to provide the desired product as a thick oil that slowly solidified upon standing (52.7 g).

[00382] Step 2B: Preparation of (trans)-tert-butyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate: A solution of tert-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (52.76 g, 241 mmol) dissolved in anhydrous methylene chloride (1 L) was cooled to 0 °C and treated with triethylamine (43.6 mL, 313 mmol) followed by methanesulfonyl chloride (20.5 mL, 265 mmol). The solution was allowed to warm slowly to ambient temperature and stirred for 14 hours. The mixture was partitioned between saturated NaHCO₃ (400 mL) and methylene chloride (400 mL). The aqueous layer was extracted with

methylene chloride. The combined organic phases were washed with 1N HCl and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with hexanes:EtOAc to provide the desired product (7.24 g).

[00383] Step 2C: Preparation of (cis)-tert-butyl 4-azido-3-fluoropiperidine-1-carboxylate: Sodium azide (4.045 g, 62.22 mmol) was added to a solution of (trans)-tert-butyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate (3.700 g, 12.44 mmol) dissolved in DMF (25 mL). The reaction was heated to 115 °C for 24 hours. The mixture was cooled and diluted with water and methylene chloride. After separation, the organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo to provide the desired product (quantitative yield).

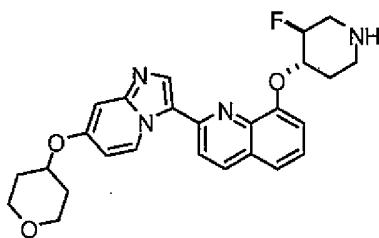
[00384] Step 2D: Preparation of (cis)-tert-butyl 4-amino-3-fluoropiperidine-1-carboxylate: Palladium on carbon (10%, 0.876 g, 0.823 mmol) was added to a solution of (cis)-tert-butyl 4-azido-3-fluoropiperidine-1-carboxylate (2.01 g, 8.23 mmol) dissolved in THF and EtOH (1:1, 82 mL). The reaction was placed under a hydrogen atmosphere (balloon pressure) and stirred for 2 hours. The mixture was filtered through GF/F paper and concentrated in vacuo. The amine was purified on a Varian Bond Elut SCX column, eluting with methylene chloride followed by a solution of MeOH containing 6% aqueous NH₄OH. The second eluant was concentrated in vacuo to provide the desired product (642 mg). MS ESI (+) m/z 218.8 (M+1) detected.

[00385] Step 2E: Preparation of (cis)-tert-butyl 3-fluoro-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ylamino)piperidine-1-carboxylate: (cis)-tert-Butyl 4-amino-3-fluoropiperidine-1-carboxylate (0.040 g, 0.18 mmol) was combined with 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yl trifluoromethanesulfonate (Steps 1A - 1D; 0.065 g, 0.140 mmol), micronized Cs₂CO₃ (0.064 g, 0.197 mmol), BINAP-racemic (0.0087 g, 0.014 mmol) and Pd₂dba₃ (0.0064 g, 0.0070 mmol). The mixture was treated with toluene (0.75 mL), degassed with argon and heated to reflux for 16 hours. The reaction was cooled, diluted with CHCl₃ and purified by silica gel chromatography, eluting with a gradient from 1-20% (6% NH₄OH in MeOH)/ethyl acetate to provide the desired product (82 mg). MS ESI (+) m/z 536.1 (M+1) detected.

[00386] Step 2F: Preparation of N-((cis)-3-fluoropiperidin-4-yl)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-amine: (cis)-tert-Butyl 3-fluoro-4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ylamino)piperidine-1-carboxylate (0.050 g, 0.093 mmol) was dissolved in MeOH (1 mL) the solution was treated with 4 M

hydrogen chloride in dioxane (0.583 ml, 2.33 mmol). The mixture was stirred at ambient temperature for 4 hours, then concentrated in vacuo. The residue was redissolved and re-concentrated from MeOH three times. This material was purified by silica gel chromatography, eluting with (6% NH₄OH in MeOH)/ethyl acetate to provide the desired product (16 mg). ¹H NMR (400 MHz, CDCl₃) δ 9.89 (d, 1H), 8.14 (s, 1H), 8.05 (d, 1H), 7.77 (d, 1H), 7.38-7.29 (m, 1H), 7.08 (d, 1H), 7.02 (s, 1H), 6.85-6.74 (m, 2H), 6.30 (d, 1H), 4.89 (d, J = 49 Hz, 1H), 4.26-4.19 (m, 2H), 3.87-3.78 (m, 2H), 3.79-3.69 (m, 1H), 3.54-3.42 (m, 1H), 3.48 (s, 3H), 3.27-3.18 (m, 1H), 3.04-2.87 (dd, 1H), 2.79 (t, 1H), 2.17-2.09 (m, 1H), 2.00-1.86 (brd, 1H), 1.81-1.67 (m, 1H), 1.30-1.22 (m, 1H).

Example 32



8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(tetrahydro-2H-pyran-4-yloxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00387] 1. Preparation of (trans)-benzyl 4-(2-chloroquinolin-8-yloxy)-3-fluoropiperidine-1-carboxylate

[00388] Step 1A: Preparation of (trans)-tert-butyl 3-fluoro-4-(quinolin-8-yloxy)piperidine-1-carboxylate: To a solution of quinolin-8-ol (3.50 g, 24.1 mmol) in 60 mL DMF was added cesium carbonate (23.6 g, 72.3 mmol), followed by (cis)-tert-butyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate (8.24 g, 27.7 mmol). The reaction mixture was heated in a 100 °C sand bath and stirred 20 hours. The reaction mixture was cooled to ambient temperature, filtered through GF/F paper topped with compressed Celite, rinsed with DMF, and concentrated. The crude was purified on silica gel (Biotage 40M, 9:1 DCM:EtOAc until the product eluted, then 2:1 DCM:EtOAc) to give (trans)-tert-butyl 3-fluoro-4-(quinolin-8-yloxy)piperidine-1-carboxylate (0.701 g, 2.02 mmol, 42 % yield). LC/MS ESI (+) m/z 347 (M+1) detected.

[00389] Step 1B: Preparation of 8-((trans)-3-fluoropiperidin-4-yloxy)quinoline dihydrochloride: To a solution of (trans)-tert-butyl 3-fluoro-4-(quinolin-8-yloxy)piperidine-1-carboxylate (5.4 g, 15.6 mmol) in 100 mL DCM was added neat TFA (24.0 ml, 311.78 mmol). The reaction mixture was stirred at ambient temperature for 4 hours, after which it was

concentrated. The resulting residue was dissolved in 40 mL DCM, and this solution was added dropwise by addition funnel to a flask containing vigorously stirring 60 mL 2 M HCl in ether in 500 mL ether, causing precipitation. The solids were isolated by filtration through a medium pore glass fritted funnel by forcing solvent through the frit with nitrogen pressure, rinsed with ether, and dried in vacuo to give 8-(trans-3-fluoropiperidin-4-yloxy)quinoline dihydrochloride (6.6 g, 21 mmol) as a solid which was used without further purification in the next step. LC/MS ESI (+) m/z 247 (M+H)⁺ detected.

[00390] Step 1C: Preparation of (trans)-benzyl 3-fluoro-4-(quinolin-8-yloxy)piperidine-1-carboxylate: To a 0 °C solution of 8-((trans)-3-fluoropiperidin-4-yloxy)quinoline dihydrochloride (6.6 g, 26.8 mmol) and TEA (18.7 ml, 134.0 mmol) in 134 mL DCM was added benzyl carbonochloridate (4.4 ml, 29.5 mmol). The reaction mixture was stirred 15 minutes at 0 °C, then warmed to ambient temperature and stirred another 16 hours. Water was added, and the mixture was extracted with DCM. The combined extracts were dried (Na₂SO₄), filtered, and concentrated. The crude was purified on silica gel (Biotage 40M, loaded with 4:1 hexanes:ethyl acetate and 500 mL flushed, then gradient to 1:1 hexanes:ethyl acetate) to give (trans)-benzyl 3-fluoro-4-(quinolin-8-yloxy)piperidine-1-carboxylate (5.2 g, 13.67 mmol, 51.01 % yield) as an oil. MS APCI (+) m/z 381 (M+1) detected.

[00391] Step 1D: Preparation of 8-((trans)-1-(benzyloxycarbonyl)-3-fluoropiperidin-4-yloxy)quinoline 1-oxide: To a 0 °C solution of (trans)-benzyl 3-fluoro-4-(quinolin-8-yloxy)piperidine-1-carboxylate (1.0 g, 2.63 mmol) in 20 mL CHCl₃ and 2 mL MeOH was added 77% max. mCPBA in 4 X 250 mg portions. The reaction mixture was stirred 20 minutes, then another 2 X 250 mg portions of 77 % max. mCPBA was added (total 77 % max. mCPBA (1.51 g, 6.57 mmol)). The reaction mixture was stirred 10 minutes, warmed to ambient temperature, and stirred another 3 hours, after which it was cooled to 0 °C. Another 2 equivalents of 77 % max. mCPBA was added in 4 equal portions, and the reaction mixture was warmed to ambient temperature and stirred an additional 1.5 hours. The reaction mixture was cooled to 0 °C, and saturated Na₂S₂O₃ was added, followed by saturated NaHCO₃. The mixture was stirred 10 minutes, then warmed to ambient temperature and stirred another 30 minutes. Solid NaCl was added, and the mixture was extracted with CHCl₃. The combined extracts were dried (Na₂SO₄), filtered, concentrated, and dried in vacuo to give 8-((trans)-1-(benzyloxycarbonyl)-3-fluoropiperidin-4-yloxy)quinoline 1-oxide (1.0 g, 2.52 mmol, 96.0 % yield), which was used without further purification in the next step.

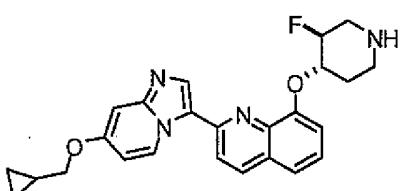
[00392] Step 1E: Preparation of (trans)-benzyl 4-(2-chloroquinolin-8-yloxy)-3-fluoropiperidine-1-carboxylate: To a 0 °C solution of 4 mL 1:1 DMF:toluene was added neat POCl₃ (0.360 ml, 3.94 mmol). The reaction mixture was warmed to ambient temperature, stirred 10 minutes, and then cooled to 0 °C. A solution of 8-((trans)-1-(benzyloxycarbonyl)-3-fluoropiperidin-4-yloxy)quinoline 1-oxide (1.04 g, 2.62 mmol) in 1.2 mL 1:1 DMF:toluene was added dropwise by syringe to the reaction mixture, and the reaction mixture was heated in a 110 °C sand bath and stirred for 1 hours. The reaction mixture was cooled to ambient temperature and added dropwise to a stirring ice/saturated NaHCO₃ mixture. The mixture was stirred 20 minutes, then extracted with DCM, and the combined extracts were dried (Na₂SO₄), filtered, and concentrated. The crude was purified on silica gel (Biotage 40S, loaded with 12:1 hexanes:ethyl acetate, flushed 300 mL, then gradient to 5:1 hexanes:ethyl acetate) to give (trans)-benzyl 4-(2-chloroquinolin-8-yloxy)-3-fluoropiperidine-1-carboxylate (0.563 g, 1.36 mmol, 51.7 % yield) as a syrup. MS APCI (+) m/z 415 (M+1) detected.

[00393] 2. Preparation of 8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(tetrahydro-2H-pyran-4-yloxy)imidazo[1,2-a]pyridin-3-yl)quinoline dihydrochloride

[00394] Step 2A: Preparation of 7-(tetrahydro-2H-pyran-4-yloxy)imidazo[1,2-a]pyridine: Prepared according to the procedure for Example 1, Steps 1A-C, using tetrahydro-2H-pyran-4-ol in place of 2-methoxyethanol. MS APCI (+) m/z 219 (M+1) detected.

[00395] Step 2B: Preparation of (trans)-benzyl 3-fluoro-4-(2-(7-(tetrahydro-2H-pyran-4-yloxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: Prepared according to the procedure used for Example 1, Step D, using 7-(tetrahydro-2H-pyran-4-yloxy)imidazo[1,2-a]pyridine in place of 7-(2-methoxyethoxy)imidazo[1,2-a]pyridine and (trans)-benzyl 4-(2-chloroquinolin-8-yloxy)-3-fluoropiperidine-1-carboxylate in place of 2,8-dibromoquinoline. MS APCI (+) m/z 597 (M+1) detected.

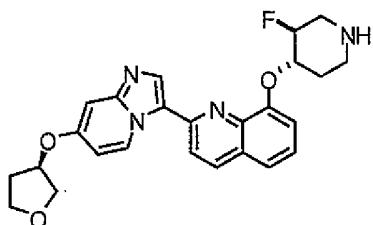
Example 33



2-(7-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline

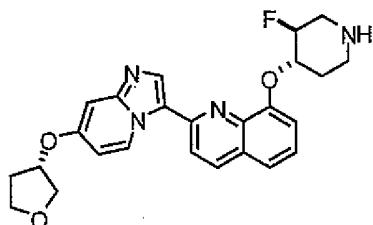
[00396] Prepared according to the procedure of Example 32, using cyclopropylmethanol in place of tetrahydro-2H-pyran-4-ol. MS APCI (+) m/z 433 (M+1) detected.

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Example 34

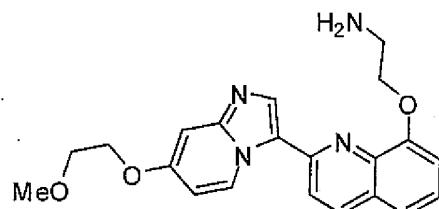
8-((trans)-3-Fluoropiperidin-4-yloxy)-2-(7-((R)-tetrahydrofuran-3-yloxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00397] Prepared according to the procedure of Example 32, using (R)-tetrahydrofuran-3-ol in place of tetrahydro-2H-pyran-4-ol. The title compound was isolated as a 1:1 mixture of diastereomers. MS APCI (+) m/z 449 (M+1) detected.

Example 35

8-((trans)-3-Fluoropiperidin-4-yloxy)-2-(7-((S)-tetrahydrofuran-3-yloxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00398] Prepared according to the procedure of Example 32, using (S)-tetrahydrofuran-3-ol in place of tetrahydro-2H-pyran-4-ol. The title compounds was isolated as a 1:1 mixture of trans diastereomers. MS APCI (+) m/z 449 (M+1) detected.

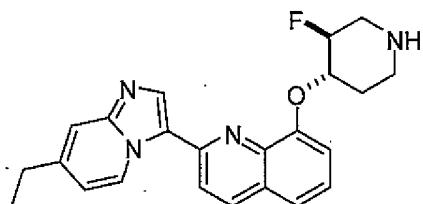
Example 36

2-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)ethanamine

[00399] To 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (50 mg, 0.15 mmol) in DMF (3 mL) was added 4 angstrom molecular sieves (2 g), tert-butyl 2-bromoethylcarbamate (40 mg, 0.18 mmol), t-butylammonium iodide (3 mg) and cesium hydroxide hydrate (50 mg, 0.30 mmol). The reaction mixture was stirred overnight, then dilute

with EtOAc/H₂O (10 mL/10 mL). The aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated to give crude, N-Boc-protected product, to which was added DCM (1 mL) and TFA (1 mL). This mixture was stirred for 30 minutes and then concentrated. The residue was purified by silica gel chromatography, eluting with DCM/MeOH/NH₄OH (10:1:0.1) to provide the desired product (20 mg). APCI (+) m/z 379.2 (M+1) detected.

Example 37



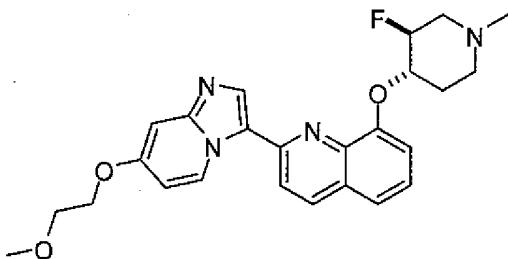
2-(7-ethylimidazo[1,2-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline

- [00400] 1. Preparation of 2-(7-ethylimidazo[1,2-a]pyridin-3-yl)quinolin-8-ol
- [00401] Step 1A: Preparation of 7-ethylimidazo[1,2-a]pyridine: A mixture of 4-ethylpyridin-2-amine (3.21 g, 8.19 mmol), and chloroacetaldehyde (50% aqueous solution, 2.6 ml, 10.5 mmol) in EtOH (10 ml) was refluxed vigorously for 12 hours. The reaction mixture was concentrated, and the residue was suspended in saturated aqueous sodium bicarbonate solution. The aqueous mixture was extracted with CH₂Cl₂ and EtOAc, and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated to afford the desired product (1.18 g, 98% yield) as a viscous oil. MS APCI (+) m/z 147.2 (M+1) detected.
- [00402] Step 1B: Preparation of 8-(benzyloxy)-2-(7-ethylimidazo[1,2-a]pyridin-3-yl)quinoline: A mixture of 7-ethylimidazo[1,2-a]pyridine (1.18 g, 8.06 mmol), 8-benzyloxy-2-chloroquinoline (2.17 g, 8.06 mmol), potassium carbonate (2.23 g, 16.2 mmol), palladium (II) acetate (90.5 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium (0) (466 mg, 0.40 mmol), 1,4-dioxane (33 ml) and water (0.33 ml) was heated under a nitrogen atmosphere overnight. The reaction mixture was diluted with water, extracted with CH₂Cl₂ and EtOAc, and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated to afford the desired product (3.45 g) as a solid. MS APCI (+) m/z 380.2 (M+1) detected.
- [00403] Step 1C: Preparation of 2-(7-ethylimidazo[1,2-a]pyridin-3-yl)quinolin-8-ol: A suspension of 8-(benzyloxy)-2-(7-ethylimidazo[1,2-a]pyridin-3-yl)quinoline (3.06 g, 8.06 mmol), Pearlman's catalyst (20% wt Pd, 283 mg) and ammonium formate (5.08 g, 80.6 mmol) in MeOH (50 ml) was degassed under nitrogen and heated at 80 °C for three hours, followed by

stirring at ambient temperature overnight. The reaction mixture was poured into excess water and extracted with CH₂Cl₂ and EtOAc. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (eluting with MeOH/CH₂Cl₂) to afford a mixture of starting material and desired product. This mixture was resubmitted to the original reaction conditions and refluxed for four hours. The reaction mixture was poured into excess water and extracted with CH₂Cl₂ and EtOAc. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated to afford the title compound (768 mg, 33 % yield) as a solid. MS APCI (+) m/z 290.3 (M+1) detected.

[00404] Step 2: Preparation of 2-(7-ethylimidazo[1,2-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline: Prepared according to the procedure for Example 16, using (cis)-tert-butyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate in place of tert-butyl 2-((methylsulfonyloxy)methyl)morpholine-4-carboxylate and 2-(7-ethylimidazo[1,2-a]pyridin-3-yl)quinolin-8-ol in place of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol. MS APCI (+) m/z 391.2 (M+1) detected.

Example 38

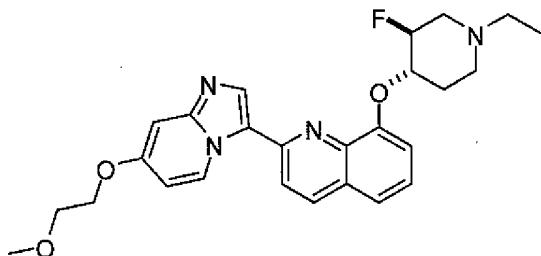


8-((trans)-3-fluoro-1-methylpiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00405] To a solution of 8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline (Example 20; 185 mg, 0.42 mmol) in CH₂Cl₂ (5 mL) was added formaldehyde (316 µL, 37% in water, 4.2 mmol) followed by acetic acid (30 µL, 0.51 mmol) and sodium triacetoxyborohydride (270 mg, 1.27 mmol). The mixture was stirred vigorously at ambient temperature for 48 hours, then treated with 10% aq. K₂CO₃ (20 mL) and stirred for 10 minutes. The mixture was extracted with CH₂Cl₂, and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash column chromatography using gradient elution (CH₂Cl₂ to 2% MeOH/CH₂Cl₂ to 5% MeOH/CH₂Cl₂) then dissolved in CHCl₃ (5 mL) and treated with 4N HCl/dioxane (2 mL). After stirring for 20 minutes at ambient temperature the mixture was

concentrated. The residue was triturated with ether, filtered and dried in vacuo to provide 136 mg (61%) of desired product as the di-HCl salt as a solid. MS APCI (+) m/z 451.2 (M+1) detected.

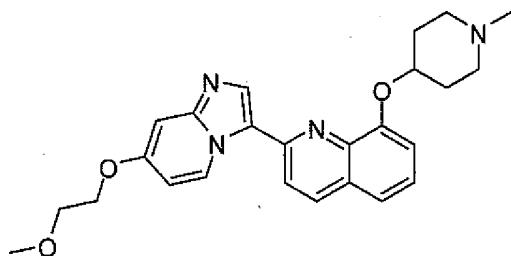
Example 39



8-((trans)-1-ethyl-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00406] Prepared from 8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline according to the procedure for Example 29, using acetaldehyde in place of formaldehyde. MS APCI (+) m/z 465.1 (M+1) detected.

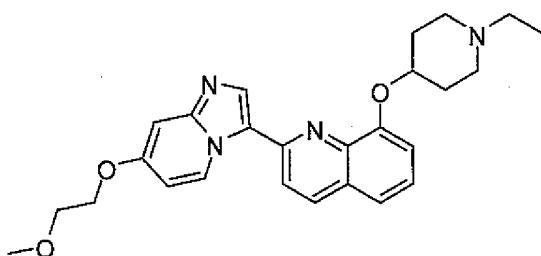
Example 40



2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(1-methylpiperidin-4-yloxy)quinoline

[00407] Prepared according to the procedure for Example 38, using 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-(piperidin-4-yloxy)quinoline (prepared as in Example 3) in place of 8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline. MS APCI (+) m/z 433.2 (M+1) detected.

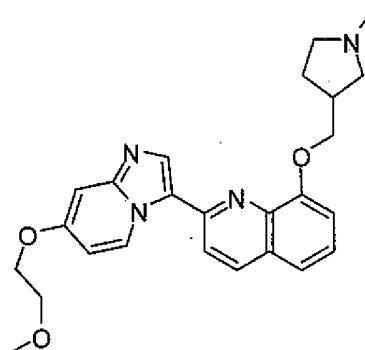
Example 41



8-(1-ethylpiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00408] Prepared according to the procedure for Example 38, using acetaldehyde in place of formaldehyde. MS APCI (+) m/z 447.1 (M+1) detected.

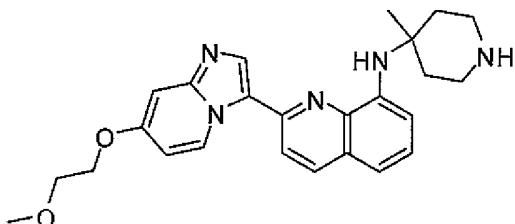
Example 42



2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-8-((1-methylpyrrolidin-3-yl)methoxy)quinoline

[00409] To a solution of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (300 mg, 0.90 mmol) in anhydrous THF (15 ml) were added at ambient temperature under a nitrogen atmosphere triphenylphosphine (352 mg, 1.34 mmol), (1-methylpyrrolidin-3-yl)methanol (155 mg, 1.34 mmol) and diethyl azodicarboxylate (0.21 ml, 1.34 mmol). The reaction mixture was stirred at ambient temperature under nitrogen atmosphere overnight. The mixture was treated with saturated aqueous sodium bicarbonate solution (20 mL) and extracted with CH₂Cl₂ and EtOAc. The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated to afford the crude product. The crude product was purified by column chromatography on silica gel (elution with 10% MeOH/CH₂Cl₂) to afford partially purified product. This material was purified by silica gel chromatography (eluting with 10% 7N NH₃/MeOH/CH₂Cl₂) to provide the title compound (34.2 mg, 9 % yield) as a solid. MS ESI (+) m/z 433.2 (M+1) detected.

Example 43

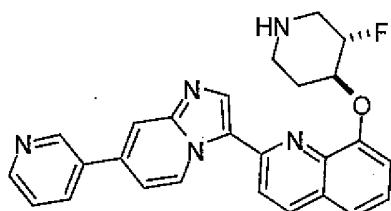


2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-N-(4-methylpiperidin-4-yl)quinolin-8-amine

[00410] Step A: Preparation of tert-butyl 4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ylamino)-4-methylpiperidine-1-carboxylate: Prepared according the procedure for Example 31, Step 2E, using tert-butyl 4-amino-4-methylpiperidine-1-carboxylate (Barth, W.E.; et al.; WO 0140217) in place of (cis)-tert-butyl 4-amino-3-fluoropiperidine-1-carboxylate. MS APCI (+) m/z 532.1 (M+1) detected.

[00411] Step B: Preparation of 2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)-N-(4-methylpiperidin-4-yl)quinolin-8-amine: Prepared according to the procedure for Example 31, Step 2F, using tert-butyl 4-(2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ylamino)-4-methylpiperidine-1-carboxylate. ^1H NMR (400 MHz, CD₃OD) δ 9.83 (d, J = 7.5 Hz, 1H), 8.25-8.18 (m, 2H), 7.94 (d, J = 8.6 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.11-7.05 (m, 2H), 6.91 (dd, 1H), 4.30-4.24 (m, 2H), 3.85-3.79 (m, 2H), 3.45 (s, 3H), 3.43-3.30 (m, 4H), 2.57-2.46 (m, 2H), 2.11-1.99 (m, 2H), 1.59 (s, 3H). MS APCI (+) m/z 432.0 (M+1) detected.

Example 44



8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinoline

[00412] Step A: Preparation of 7-bromoimidazo[1,2-a]pyridine: A solution of 4-bromopyridin-2-amine (1.00 g, 5.78 mmol) and 2-chloroacetaldehyde (50% wt aqueous solution, 1.83 ml, 14.45 mmol) in absolute ethanol (9.5 ml) was refluxed for 12 hours, and then allowed to cool to ambient temperature overnight. The reaction mixture was concentrated under reduced pressure and carefully re-suspended in saturated aqueous bicarbonate solution (100 ml). The resulting mixture was extracted thoroughly with DCM and EtOAc, and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated to afford 1.31 g of a solid. The solid was purified by silica gel chromatography (eluting with 3% MeOH-chloroform) to afford the desired compound (0.808 g, 71 % yield). MS APCI (+) m/z 197.1 and 199.1 (M+1 for each isotope) detected.

[00413] Step B: Preparation of 7-(pyridin-3-yl)imidazo[1,2-a]pyridine: A suspension of potassium carbonate (0.351 g, 2.54 mmol), pyridin-3-ylboronic acid (68.6 mg, 0.558 mmol), 7-bromoimidazo[1,2-a]pyridine (0.100 g, 0.508 mmol) and tetrakis(triphenylphosphine)

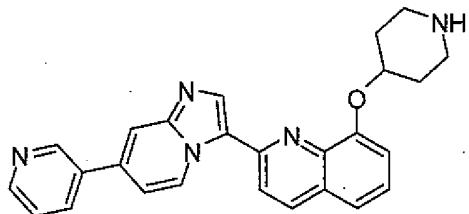
palladium (0) (29.3 mg, 0.025 mmol) in 6.5 ml of a 1:1:4.5 mixture of water:dimethylformamide:acetonitrile was degassed thoroughly under a nitrogen atmosphere, and heated at 60 °C for 18 hours. The reaction mixture was poured in water (50 ml) and extracted with dichloromethane and EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to afford a solid. The solid was purified by silica gel chromatography (eluting with 6% MeOH-chloroform) to afford the desired compound (74.1 mg, 75 % yield). MS APCI (+) m/z 196.3 (M+1) detected.

[00414] Step C: Preparation of 2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol: Prepared according to the procedure for Example 31, steps 1A to 1D using 7-(pyridin-3-yl)imidazo[1,2-a]pyridine in place of 7-(2-methoxyethoxy)-imidazo[1,2-a]pyridine.

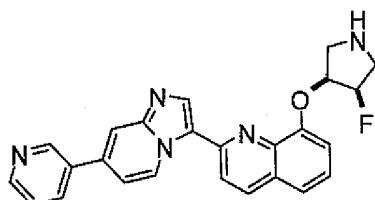
[00415] Step D: Preparation of tert-butyl trans-3-fluoro-4-(2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: A mixture of 2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (30.2 mg, 0.089 mmol), tert-butyl cis-3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate (39.8 mg, 0.134 mmol) and Cs₂CO₃ (43.6 mg, 0.134 mmol) in DMA (7.78 mg, 0.089 mmol) was heated to 100 °C for 1 hour. The reaction mixture was cooled to ambient temperature and diluted with water and EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative TLC, eluting with 10% MeOH 0.5% NH₄OH in DCM to provide the desired product (22 mg, 46 % yield).

[00416] Step E: Preparation of 8-(trans-3-fluoropiperidin-4-yloxy)-2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinoline: tert-Butyl trans-3-fluoro-4-(2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (22 mg, 0.041 mmol) was added to 2 ml DCM at ambient temperature. TFA (2 mL) was added and the reaction was stirred for 1 hour, then diluted with DCM and water. The mixture was washed with 1N NaOH amine and extracted with DCM, followed by extraction with 20% IPA/Chloroform. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative TLC, eluting with 15 % MeOH/0.5 % NH₄OH in DCM to provide the desired product as a film (5.6 mg, 31 % yield). MS APCI (+) m/z 440.1(M+1) detected.

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Example 458-(piperidin-4-yloxy)-2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinoline

[00417] Compound was isolated during purification of the compound prepared according to Example 44. MS APCI (+) m/z 422.1 (M+I) detected.

Example 468-((cis)-4-fluoropyrrolidin-3-yloxy)-2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinoline

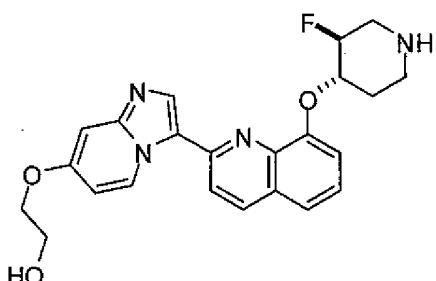
[00418] Step A: Preparation of (trans)-naphthalen-2-ylmethyl 3-fluoro-4-hydroxypyrrolidine-1-carboxylate: A plastic (HDPE) bottle was charged with naphthalen-2-ylmethyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (945 mg, 3.509 mmol) and HF-pyridine (264 μ L, 10.527 mmol) in DCM (17.55 ml, 3.509 mmol) and the reaction mixture was stirred for 36 hours at ambient temperature. The reaction was slowly quenched with aqueous saturated NaHCO₃ and diluted with water and DCM. The reaction mixture was extracted with DCM, and the combined organics layers were dried over Na₂SO₄ and concentrated to give the product as an oil (237 mg, 23.3% yield)

[00419] Step B: Preparation of (trans)-naphthalen-2-ylmethyl 3-fluoro-4-(tosyloxy)pyrrolidine-1-carboxylate: A flask was charged with (trans)-naphthalen-2-ylmethyl 3-fluoro-4-hydroxypyrrolidine-1-carboxylate (237 mg, 0.819 mmol), TEA (0.343 ml, 2.458 mmol) and DMAP (10.0 mg, 0.082 mmol) in DCM (4.3 ml, 0.86 mmol). The reaction mixture was cooled to 0 °C, and 4-methylbenzene-1-sulfonyl chloride (234 mg, 1.23 mmol) was added. The reaction was warmed to ambient temperature and stirred for 3 hours. The reaction was diluted with water and extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography, eluting with 0-5% MeOH in DCM to give the product as an oil (160 mg, 44% yield).

[00420] Step C: Preparation of (cis)-naphthalen-2-ylmethyl 3-fluoro-4-(2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-1-carboxylate: A flask was charged with 2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (97.7 mg, 0.289 mmol), (trans)-naphthalen-2-ylmethyl 3-fluoro-4-(tosyloxy)pyrrolidine-1-carboxylate (160 mg, 0.361 mmol) and Cs₂CO₃ (282 mg, 0.866 mmol) in DMF (1443 μl, 0.289 mmol). The mixture was heated to 70 °C for 4 hours, then diluted with water and EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography to give the desired product (50 mg, 28 % yield). MS APCI (+) m/z 610.2 (M+1) detected.

[00421] Step D: Preparation of 8-((cis)-4-fluoropyrrolidin-3-yloxy)-2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinoline: A solution of cis-naphthalen-2-ylmethyl 3-fluoro-4-(2-(7-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-1-carboxylate (2.0 mg, 0.003 mmol) in 1 ml DCM was cooled to 0 °C and 1 ml TFA was added. The mixture was stirred for 16 hours at ambient temperature and then concentrated. The residue was purified by preparative TLC, eluting with 15% MeOH/0.5% NH₄OH in chloroform to give the title compound as a film (1.1 mg, 78% yield). MS APCI (+) m/z 426.2 (M+1) detected.

Example 47

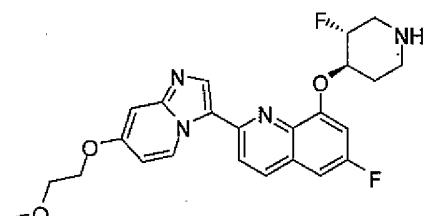


2-(3-(8-(trans-3-fluoropiperidin-4-yloxy)quinolin-2-yl)imidazo[1,2-a]pyridin-7-yloxy)ethanol

[00422] To a flask containing 8-(3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline (Prepared according to Example 20; 0.062 g, 0.14 mmol) was added CH₂Cl₂ (14 mL) and the solution was cooled to -78 °C. BBr₃ (1.0M in CH₂Cl₂, 0.71 ml, 0.71 mmol) was added dropwise and the reaction stirred at -78 °C for 1 hour, then slowly warmed to 0 °C over 2.0 hours, then warmed to ambient temperature and stirred for 0.5 hours. The reaction was quenched by the addition of a saturated aqueous NaHCO₃ solution (15 mL) and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ and the combined organic phases were washed with brine and dried over Na₂SO₄. The mixture was filtered and concentrated *in vacuo* and purified via column chromatography

(6% NH₄OH in MeOH/CH₂Cl₂, 2% to 20 % linear gradient) to afford 0.015 g (0.25%) of the title compound as a solid. MS APCI (+) m/z 423.2 [M+H]⁺ detected.

Example 48



6-fluoro-8-((3R,4R)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00423] Step 1A: Preparation of 6-fluoro-2-methylquinolin-8-ol: 2-Amino-5-fluorophenol (13.0 g, 102 mmol) was dissolved in 6N HCl (78 mL) and heated to reflux. The solution was treated with (E)-but-2-enal (8.8 ml, 107 mmol) in 1 mL portions over 1 hour. The reaction was heated at reflux for 13 hours. The reaction mixture was cooled and adjusted to pH 8 with concentrated NH₄OH. The reaction was diluted with ethyl acetate, stirred for 30 minutes then filtered through a nylon membrane (0.45 µM). The filtrate was separated and the aqueous was washed with ethyl acetate. The combined organics were washed with saturated NaHCO₃, saturated NaCl, dried over Na₂SO₄ and concentrated *in vacuo* to a thick dark oil (19 g). MS APCI (+) m/z 178.1 (M+1) detected.

[00424] Step 1B: Preparation of 6-fluoro-2-methyl-8-(triisopropylsilyloxy)quinoline: 6-Fluoro-2-methylquinolin-8-ol (19.0 g, 107 mmol) was dissolved in methylene chloride (300 mL) and treated with 1H-imidazole (10.9 g, 160 mmol) and triisopropylsilyl trifluoromethanesulfonate (33.1 ml, 123 mmol). The reaction was stirred at ambient temperature for 13 hours. The reaction mixture was quenched with saturated NH₄Cl and separated. The organic layer was washed twice with saturated NH₄Cl, dried over Na₂SO₄ and concentrated *in vacuo* (35 g).

[00425] Step 1C: Preparation of 6-fluoro-8-(triisopropylsilyloxy)quinoline-2-carbaldehyde: 6-Fluoro-2-methyl-8-(triisopropylsilyloxy)quinoline (1.76 g, 5.29 mmol) was dissolved in dioxane (58 mL) and water (0.49 mL). The reaction was treated with selenium dioxide (0.76 g, 6.8 mmol) and the mixture was heated to reflux for 13 hours. The mixture was cooled and filtered through GF/F paper. The filtered solids were washed with Et₂O then all the filtrates were concentrated *in vacuo*. The crude mixture was chromatographed on silica gel, eluting with a gradient of 1-5% Et₂O/hexanes, (0.515 g). ¹H NMR (400 MHz, CDCl₃) δ 10.19

(s, 1H), 8.18 (d, $J = 8.7$ Hz, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 7.14-7.08 (m, 1H), 7.06-7.00 (m, 1H), 1.52-1.41 (m, 3H), 1.16 (d, 18H).

[00426] Step 1D: Preparation of 6-fluoro-2-(2-methoxyvinyl)-8-(triisopropylsilyloxy)quinoline: (Methoxymethyl)triphenylphosphonium chloride (8.355 g, 24.37 mmol) was dissolved in THF (130 mL), cooled to 0 °C, and treated dropwise with a solution of 1M KOtBu in THF (26.5 ml, 26.5 mmol). The mixture was warmed and stirred at ambient temperature for 15 minutes. A solution of 6-fluoro-8-(triisopropylsilyloxy)quinoline-2-carbaldehyde (7.70 g, 22.1 mmol) dissolved in THF (15 mL) was added. The reaction was stirred at ambient temperature for 10 hours. The mixture was concentrated *in vacuo* and applied directly to a column of SiO₂ eluting with a stepped gradient from 1-4% Et₂O/hexanes, (4.75 g). ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, $J = 8.6$ Hz, 1H), 7.74 (d, $J = 13$ Hz, 1H), 7.23 (d, $J = 8.6$ Hz, 1H), 6.93 (dd, $J_1 = 2.8$ Hz, $J_2 = 8.7$ Hz, 1H), 6.88 (dd, $J_1 = 2.7$ Hz, $J_2 = 10.2$ Hz, 1H), 6.02 (d, $J = 12.5$ Hz, 1H), 3.77 (s, 3H), 1.47-1.38 (m, 3H), 1.15 (d, 18H).

[00427] Step 2A: Preparation of 2-chloro-4-(2-methoxyethoxy)pyridine: A mixture of 2-chloro-4-nitropyridine (43.6 g, 275 mmol) and 2-methoxyethanol (325 ml, 425 mmol) was cooled to 0 °C. Potassium 2-methylpropan-2-olate (35.7 g, 302 mmol) was added and the resulting mixture was stirred while warming to ambient temperature over 2 hours. The reaction mixture was concentrated under reduced pressure followed by dilution with 500 ml of water. The resulting mixture was extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to produce the desired compound as an oil (50.2 g). MS APCI (+) m/z 188 and 189.9 (M+1 of each isotope) detected.

[00428] Step 2B: Preparation of 4-(2-methoxyethoxy)pyridin-2-amine: A steady stream of nitrogen was passed through a mixture of 2-chloro-4-(2-methoxyethoxy)pyridine (50.1 g, 267 mmol), Pd₂dba₃ (4.89 g, 5.34 mmol), XPHOS (5.09 g, 10.7 mmol) and tetrahydrofuran (445 ml) for 10 minutes. To the resulting degassed mixture was added lithium bis(trimethylsilyl)amide (561 ml, 561 mmol). After addition, the resulting mixture was heated to 60 °C for 18 hours. The reaction was cooled to ambient temperature and diluted with 1 N hydrochloric acid (200 mL). The resulting solution was washed twice with 500 ml of methyl-tert-butyl ether. The pH of the aqueous layer was adjusted to 11 with 6 N NaOH and extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to yield title compound (35 g) MS APCI (+) m/z 169 (M+1) detected.

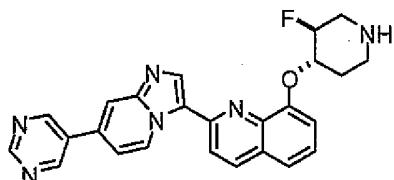
[00429] Step 2C: Preparation of 6-fluoro-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol: 6-Fluoro-2-(2-methoxyvinyl)-8-(triisopropylsilyloxy)quinoline (2.5 g, 6.6 mmol) was dissolved in THF (10.3 mL) and water (2.6 mL) and cooled to 0 °C. The solution was treated dropwise with a solution of freshly recrystallized N-bromosuccinimide (1.24 g, 6.99 mmol) dissolved in THF (7 mL) and water (1.75 mL). The reaction was stirred at 0 °C for 20 minutes then warmed and stirred at ambient temperature for 2.5 hours. The reaction was treated with 4-(2-methoxyethoxy)pyridin-2-amine (1.12 g, 6.65 mmol) and the mixture was heated to reflux overnight. The mixture was cooled and solids formed in the flask. Chloroform (50 mL), ethyl acetate (300 mL), and water (50 mL) were added to disperse the solids and the undissolved solids were collected by filtration and washed with ethyl acetate and water, then air-dried, (1.2 g). MS APCI (+) m/z 354.1 (M+1) detected.

[00430] Step A: Preparation of (3R,4R)-naphthalen-2-ylmethyl 3-fluoro-4-(6-fluoro-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: (3R,4S)-naphthalen-2-ylmethyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate (170mg, 0.44 mmol) (Example 20, Step F, derived from Peak 2), 6-fluoro-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-ol (173 mg, 0.49 mmol) and Cs₂CO₃ (290 mg, 0.89 mmol) were weighed into a flask and suspended in 10 mL of DMA. The reaction was then heated to 90 °C overnight. The reaction was then cooled to ambient temperature, followed by workup with water and EtOAc. The combined organic phase was concentrated in vacuo, followed by flash column chromatography (1-10% MeOH/DCM) affording the desired product as a brown semi-solid (270 mg, 0.43 mmol, 95 %). MS APCI (+) m/z 639.2 and 640.1 (M+1/+3) detected.

[00431] Step B: Preparation of 6-fluoro-8-((3R,4R)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline: Pd/C (45 mg, 0.042 mmol) 10% wet was added to a solution of (3R,4R)-naphthalen-2-ylmethyl 3-fluoro-4-(6-fluoro-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (270 mg, 0.42 mmol) in a 1:1 mixture of EtOH/EtOAc (10 mL) and 500 uL of 6 N HCl. The mixture was purged with H₂, and then allowed to stir under a balloon of hydrogen for 48 hours. The mixture was filtered through GF paper removing the desired product salt as a precipitate, with the palladium catalyst. The combined solids were washed into a beaker with 30 mL of MeOH and the palladium removed by subsequent filtration through GF filter paper. The organic phase was concentrated in vacuo, followed by flash column chromatography (1-20% MeOH/DCM

(4% NH₄OH). The resulting product was dissolved in chloroform and subject to four equivalents of 4 M HCl in dioxane. The desired product was then isolated as the bis-HCl salt. MS APCI (+) m/z 455.2 (M+1) detected.

Example 49

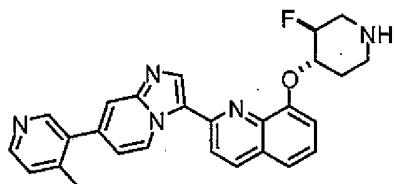


8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(pyrimidin-5-yl)imidazo[1,2-a]pyridin-3-yl)quinoline

[00432] Step A: Preparation of 7-(pyrimidin-5-yl)imidazo[1,2-a]pyridine: Prepared according to the procedure for Example 44, Step B using pyrimidin-5-ylboronic acid in place of pyridin-3-ylboronic acid. MS APCI (+) m/z 197 (M+1) detected.

[00433] Step B: Preparation of benzyl trans-3-fluoro-4-(2-(7-(pyrimidin-5-yl)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: Prepared according to the procedures of Example 44, steps C to D, using 7-(pyrimidin-5-yl)imidazo[1,2-a]pyridine in place of 7-(pyridin-3-yl)imidazo[1,2-a]pyridine. MS APCI (+) m/z 575 (M+1) detected.

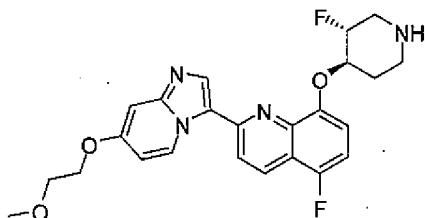
[00434] Step C. Preparation of 8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(pyrimidin-5-yl)imidazo[1,2-a]pyridin-3-yl)quinoline: To a solution of (trans)-benzyl 3-fluoro-4-(2-(7-(pyrimidin-5-yl)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (0.005 g, 0.009 mmol) in 0.80 mL 1:1 THF:EtOH was added 5% Pd/C (0.009 g, 0.004 mmol). Hydrogen was bubbled through the reaction mixture, and the reaction was stirred under a hydrogen balloon for 15 hours at ambient temperature. The reaction mixture was then vacuum filtered through compressed Celite, rinsed with MeOH, and the filtrate was concentrated and dried in vacuo. The resulting solids were dissolved in 1 mL DCM, and this solution was added dropwise to a vigorously stirring solution of 1 mL 2 M HCl in ether in 10 mL ether, causing precipitation. The mixture was concentrated and dried in vacuo to give the title compound as the dihydrochloride salt (0.002 g, 0.003 mmol, 40 % yield) as a solid. MS APCI (+) m/z 441 (M+1) detected.

Example 50

8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(4-methylpyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinoline

[00435] Step A: Preparation of (trans)-benzyl 3-fluoro-4-(2-(7-(4-methylpyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: Prepared according the procedures of Example 44, steps A through D, using 4-methyl-pyridin-3-ylboronic acid in place of pyridin-3-ylboronic acid. MS APCI (+) m/z 588 (M+1) detected.

[00436] Step B: Preparation of 8-((trans)-3-fluoropiperidin-4-yloxy)-2-(7-(4-methylpyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)quinoline: The Cbz group can be removed using the conditions described for Example 49, Step C to give the title compound.

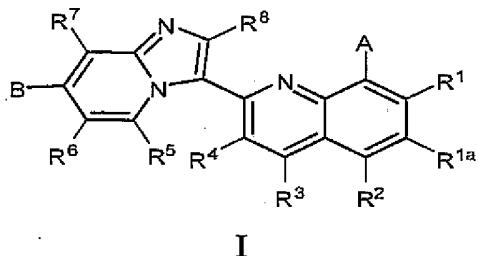
Example 51

5-fluoro-8-((3R,4R)-3-fluoropiperidin-4-yloxy)-2-(7-(2-methoxyethoxy)imidazo[1,2-a]pyridin-3-yl)quinoline

[00437] Prepare according to the procedure of Example 48, using 2-amino-4-fluorophenol in place of 2-amino-5-fluorophenol.

What is claimed is:

1. A compound of general Formula I:



5 or a pharmaceutically acceptable salt thereof, wherein:

A is $-Z-(CH_2)_p-(hetCyc^{2a})$, $-Z-(hetCyc^{2b})$, $Z-R^{10}$ or $Z-R^{11}$;

Z is O or NH;

p is 0, 1, or 2;

hetCyc^{2a} is a 5 or 6 membered heterocyclic ring optionally substituted with
10 one or more R⁹ groups;

hetCyc^{2b} is a 7-12 membered spirocyclic or bridged heterobicyclic ring system optionally substituted with one or more R⁹ groups;

R¹⁰ is (1-6C)alkyl substituted with NR'R";

R¹¹ is (5-6C)cycloalkyl substituted with NR'R";

15 B is H, CN, OR^h, Ar¹, hetAr², C(O)NR'Rⁱ, C(O)-hetCyc³, C(O)NH(1-6C alkyl)-hetCyc³, C(O)(1-6C alkyl)-hetCyc³, SR^k, SO₂N(1-6C alkyl)₂, (1-6C alkyl)NR'R" or (1-3C)alkyl;

R¹, R², R³ and R⁴ are independently H, F, Cl, CN, Me, Et, isopropyl, cyclopropyl, C(O)NR'R", CH₂OH, or hetAr³;

20 R^{1a} is H, F, Cl, or Me;

R⁵, R⁶, R⁷ and R⁸ are independently H, F, Cl, CN or Me;

each R⁹ is independently selected from halogen, CN, CF₃, (1-6C)alkyl, NR^aR^b, -(1-6C alkyl)NR^aR^c, OR^a, (1-6C alkyl)OR^a [optionally substituted with amino], C(O)NR^aR^c, C(O)(CR^xR^y)NR^aR^c, NHC(O)R^e, NHC(O)(CR^mRⁿ)NR^aR^c, NHC(O)NR^fR^g, (1-25 6C alkyl)-hetAr¹, (1-6C alkyl)-hetCyc¹, oxo, and C(O)O(1-6C alkyl);

each R^a is independently H or (1-6C)alkyl;

each R^b is independently H, (1-6C)alkyl, (1-6C alkyl)OH, (3-6C)cycloalkyl, CH₂hetAr⁴, (1-6C fluoroalkyl) or -(1-6C alkyl)-O-(1-6C alkyl),

each R^c is independently H, (1-6C)alkyl, (3-6C)cycloalkyl, or aryl;

- each R^e is independently (1-6C alkyl);
each R^f and R^g is independently H or (1-6C alkyl);
R^h is H, CF₃, (1-6C)alkyl, (1-6Calkyl)-(3-6C cycloalkyl), (1-6C alkyl)-O-(1-6C alkyl), (1-6C alkyl)OH, (1-6C alkyl)-S-(1-6C alkyl), (1-6C alkyl)NR'R'', hetCyc⁴, (1-6C alkyl)hetCyc⁴, (1-6C alkyl)aryl, or (1-6C alkyl)-hetAr⁵;
- Rⁱ is H or 1-6C alkyl;
R^j is (1-6C)alkyl, (1-6C alkyl)-O-(1-6C alkyl), or (1-6C alkyl)-OH;
R^k is (1-6C)alkyl, (3-6C)cycloalkyl, or (1-6C alkyl)-O-(1-6C alkyl);
R^m and Rⁿ are independently H or (1-6C alkyl);
R^x and R^y are independently H or (1-6C alkyl),
or R^x and R^y together with the atom to which they are attached form a cyclopropyl ring;
- Ar¹ is aryl optionally substituted with OH, O-(1-6C alkyl), C(O)₂(1-6C alkyl), or (1-6C alkyl)NR'R'';
- hetCyc¹ is a 5-6 membered heterocyclic ring which is optionally substituted with (1-6C)alkyl or OH;
- hetCyc³ and hetCyc⁴ are independently a 5 or 6 membered heterocyclic ring optionally substituted with OH or -O(1-6C alkyl);
- hetAr¹ and hetAr² are a 5-6 membered heteroaryl ring optionally substituted with one to three groups independently selected from (1-6C)alkyl, (3-6C)cycloalkyl, halogen, CN, CF₃, OCH₂F, OCF₃, O(1-6C alkyl), O(3-6C)cycloalkyl, and NR'R'';
- hetAr³ and hetAr⁴ are independently a 5-6 membered heteroaryl ring;
- hetAr⁵ is a 5-6 membered heteroaryl ring optionally substituted with (1-6C)alkyl; and
- R' and R'' are independently H or (1-6C)alkyl.
2. A compound of claim 1, wherein A is -NH(hetCyc^{2a}), -NH-(CH₂)-hetCyc^{2a}, or -NH-(CH₂)₂-hetCyc^{2a}, wherein said hetCyc^{2a} is optionally substituted with one or more R⁹ groups.
3. A compound of claim 1, wherein A is -O-hetCyc^{2a}, -O-(CH₂)-hetCyc^{2a}, or -O-(CH₂)₂-hetCyc^{2a}, wherein said hetCyc^{2a} is optionally substituted with one or more R⁹ groups.

4. A compound as defined in any of claims 1-3, wherein hetCyc^{2a} is optionally substituted with one or more R⁹ groups independently selected from halogen, -C(O)O(1-6C alkyl), (1-6C alkyl), and -OR².

5. A compound of claim 4, wherein hetCyc^{2a} is optionally substituted with one or more R⁹ groups independently selected from F, methyl, OH, -C(O)₂Me, and OMe.

6. A compound as defined in any of claims 1-5, wherein hetCyc^{2a} is a pyrrolidinyl, piperidinyl or morpholinyl ring optionally substituted with one or more R⁹ groups.

7. A compound of claim 1, wherein A is -O-hetCyc^{2a} and hetCyc^{2a} is a piperidinyl ring substituted with a fluoro group.

8. A compound of claim 1, wherein A is -NH(hetCyc^{2b}) or -O-(hetCyc^{2b}), wherein said hetCyc^{2b} is optionally substituted with one or more R⁹ groups.

9. A compound of claim 8, wherein hetCyc^{2b} is 7-11 membered bridged aza- or diaza-heterocycle optionally substituted with one or more R⁹ groups.

10. A compound according to any of claims 8-9, wherein R⁹ is selected from halogen, (1-6C alkyl), OH, and -O(1-6C alkyl).

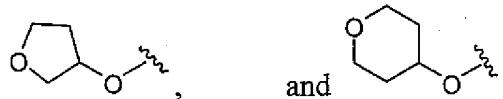
11. A compound of claim 8-10, wherein R⁹ is selected from F, Me and OH.

12. A compound of claim 1, wherein A is Z-R¹⁰.

13. A compound of claim 1, wherein A is Z-R¹¹.

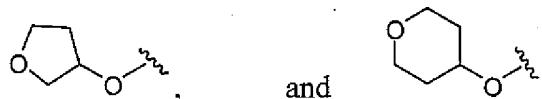
14. A compound as defined in any of claims 1-13, wherein B is selected from OR^h, (1-3C)alkyl, and hetAr².

15. A compound of claim 14, wherein B is selected from -OCH₂CH₂OCH₃, -OCH₂CH₂OH, -OCH₂(cyclopropyl), ethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl,



16. A compound as defined in any of claims 1-13, wherein B is OR^h.

17. A compound of claim 16, wherein B is selected from -OCH₂CH₂OCH₃, -OCH₂CH₂OH, -OCH₂(cyclopropyl),

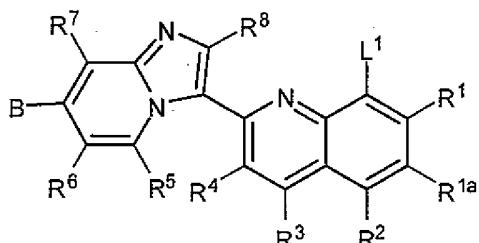


18. A compound of claim 17, wherein B is -OCH₂CH₂OCH₃.

19. A compound as defined in any of claims 1-13, wherein B is hetAr².

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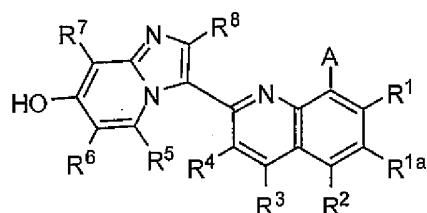
20. A compound of claim 19, wherein B is selected from 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl.
21. A compound of claim 20, wherein B is 3-pyridyl.
22. A compound as defined in any one of claims 1-21, wherein R^{1a} is H or F.
- 5 23. A compound as defined in any one of claims 1-22, wherein R² is H or F.
24. A compound as defined in any one of claims 1-23, wherein R³ is H, methyl or oxazolyl.
25. A compound as defined in any one of claims 1-24, wherein each of R⁵, R⁶, R⁷ and R⁸ is hydrogen.
- 10 26. A compound as defined in any of claims 1-25, wherein each of R¹ and R⁴ is hydrogen.
27. A compound of Formula I as defined in any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof for use in the treatment of cancer.
- 15 28. A compound of Formula I as defined in any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof for use in the treatment of fibrosis.
29. A pharmaceutical composition, which comprises a compound of Formula I as defined in any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.
30. A method of treating cancer in a mammal, which comprises administering to 20 said mammal a therapeutically effective amount of a compound of Formula I as defined in any of claims 1-26, or a pharmaceutically acceptable salt thereof.
31. A method of treating fibrosis in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I as defined in any of claims 1-26, or a pharmaceutically acceptable salt thereof.
- 25 32. A process for the preparation a compound of claim 1, which comprises:
- (a) for a compound of the Formula I wherein A is -NH-(CH₂)_n(hetCyc^{2a}), -NH-(hetCyc^{2b}), -NHR¹⁰ or -NHR¹¹, coupling a corresponding compound having the formula II



II

wherein L¹ represents a leaving group or atom, with a compound having the formula H₂N-(CH₂)_nhetCyc^{2a}, H₂N-hetCyc^{2b}, NH₂R¹⁰ or NH₂R¹¹, using a palladium catalyst and a ligand in the presence of a base; or

- (b) for a compound of Formula I where B is OR^h, reacting a corresponding compound having the Formula III

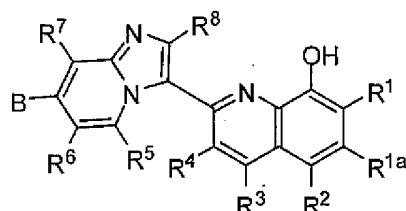


III

with a compound of the formula R^h-L² wherein L² represents a leaving group in the presence of a base; or

- (c) for a compound of Formula I where B is OR^h, reacting a corresponding compound having the Formula III with a compound having the formula R^h-OH in the presence of a coupling reagent; or

- (d) for a compound of Formula I wherein A is -O-(CH₂)_nhetCyc^{2a}, -O-hetCyc^{2b}, -OR¹⁰ or -OR¹¹, reacting a corresponding compound having the formula IV



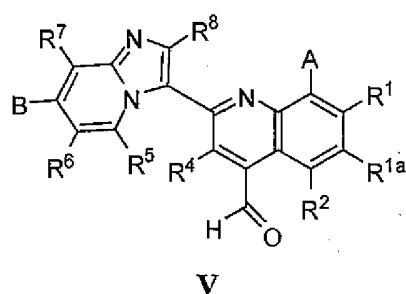
IV

with a corresponding compound having the formula HO-(CH₂)_nhetCyc^{2a}, HO-hetCyc^{2b}, HOR¹⁰ or HOR¹¹ in the presence of a coupling agent and triphenylphosphine in a suitable solvent; or

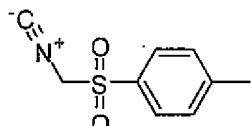
- (e) for a compound of Formula I wherein A is -O-(CH₂)_nhetCyc^{2a}, reacting a compound of Formula IV with a compound having the formula MeSO₂-O-(CH₂)_nhetCyc^{2a} in the presence of a base; or

- (f) for a compound of Formula I wherein R³ is hetAr³ and hetAr³ is oxazolyl, cyclizing a compound having the formula V

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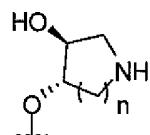


with a compound having the formula

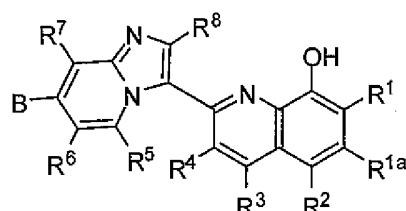


5 in the presence of a base; or

(g) for a compound of Formula I wherein A is

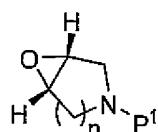


and n is 1 or 2, reacting a corresponding compound having the formula IV



IV

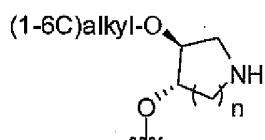
with a compound having the formula



wherein n is 1 or 2 and P¹ is an amine protecting group, in the presence of a base;

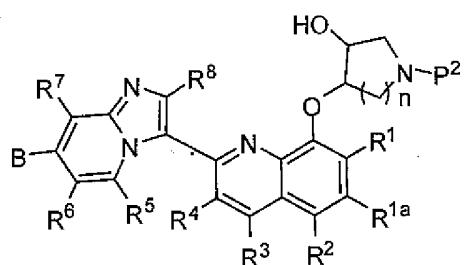
or

15 (h) for a compound of Formula I wherein A is:



and n is 1 or 2, reacting a corresponding compound having the formula VII

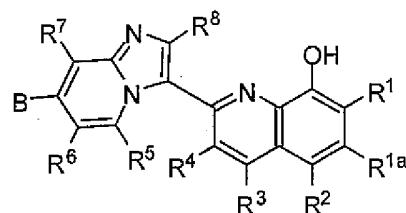
83



VII

wherein n is 1 or 2 and P² is H or an amine protecting group, with a compound having the formula (1-6C alkyl)L³ where L³ is a leaving group or atom in the presence of a base; or

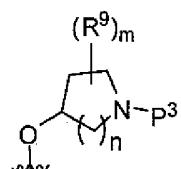
- (i) for a compound of Formula I wherein A is O-(1-6C alkyl)NR'R'', reacting a compound having the formula IV



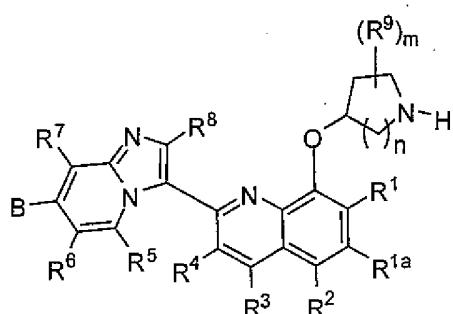
IV

with a compound having the formula L⁴-(1-6C alkyl)NR'R'' where L⁴ is a leaving group or atom, in the presence of a base and optionally in the presence of a phase transfer catalyst; or

- (j) for a compound of Formula I wherein A is:



and n is 1 or 2, P³ is H or (1-6C)alkyl, reacting a corresponding compound having the formula VIII



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with a compound having the formula HC(O)P^3 where P^3 is H or (1-6C)alkyl, in the presence of a reducing agent; and
removing any protecting group or groups and optionally forming a salt.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/058395

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D471/04 A61K31/33 A61P35/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/256309 A1 (ALTENBACH ROBERT J [US] ET AL) 17 November 2005 (2005-11-17) paragraph [0241]; claims; example 3 -----	1,27-32
<input type="checkbox"/> Further documents are listed in the continuation of Box C.		<input checked="" type="checkbox"/> See patent family annex.
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 2 July 2008		Date of mailing of the international search report 09/07/2008
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016		Authorized officer van Laren, Martijn

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box II.1

Although claims 30 and 31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US2008/058395**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/058395

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 2005256309 A1	17-11-2005	CA 2566898 A1		01-12-2005