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[Continued on next page]

(54) **Title:** TRIAZOLOPYRIDINE COMPOUNDS AS PIM KINASE INHIBITORS

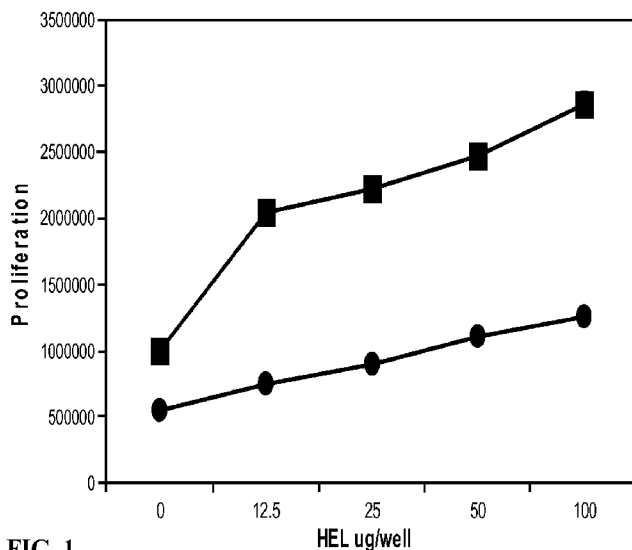
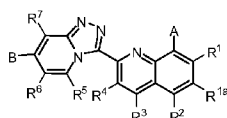


FIG. 1

(57) **Abstract:** Compounds of Formula (I), in which A, B, R¹, R^{1a}, R², R³, R⁴, R⁵, R⁶, and R⁷ have the meanings given in the specification, are receptor tyrosine inhibitors useful in the treatment of immune cell-associated diseases and disorders, such as inflammatory and autoimmune diseases.



I



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TRIAZOLOPYRIDINE COMPOUNDS AS PIM 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 triazolopyridine compounds useful in the treatment and prevention of diseases which can be treated with a PIM kinase inhibitor, including diseases mediated by PIM kinases. Particular compounds of this invention have been found to be inhibitors of PIM-1 and/or PIM-2 and/or PIM-3.

[0002] Protein kinases constitute a family of structurally related enzymes that are responsible for the control of a vast array of cellular processes.

[0003] The PIM kinase sub-family consists of three distinct serine/threonine protein kinase isoforms (PIM-1, -2 and -3) belonging to the calmodulin-dependent protein kinase-related (CAMK) group. PIM-2 and PIM-3 are respectively 58% and 69% identical to PIM-1 at the amino acid level.

[0004] 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). PIM-1 has been shown to synergize with c-Myc to drive lymphomagenesis (Breuer M., et al., Nature, 1989, 340: 61-63), and plays an important role in cytokine signaling in T-cell development (Schmidt, T., et al., EMBO J, 1998, 17:5349-5359). 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). PIM-1 has been shown to be critical for IL-6 mediated proliferation of hematopoietic cells (Hirano, T., et al. Oncogene 2000, 19: 2548-2556), as well as STAT3 mediated cell cycle progression (Shirogane, T., et al., Immunity 1999, 11:709).

[0005] Recently, it has been discovered that PIM-1 is up-regulated by Flt-3 and may play an important 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.

[0006] PIM-2 is a highly conserved serine/threonine kinase involved in cell proliferation and the prevention of apoptosis (Baytel et al., Biochim. Biophys. Acta Gene

Struct. Expr. 1442: 274 (1998)). PIM-2 is upregulated in AML, CLL, and possibly in prostate cancer.

[0007] PIM-3 is a proto-oncogene identified in pancreatic liver and colon cancers, and is an apoptotic regulator (Popivanova, B., et al., *Cancer Sci.*, 98(3): 321 (2007)).

[0008] Based upon the direct involvement of the Pim kinases in a wide variety of cancers downstream of STAT3/5 activation, it is expected that inhibition of the Pim kinases will result in inhibition of proliferation and survival of multiple cancer cell types. This would then be expected to provide a therapeutic benefit to cancer patients with a variety of cancers (both in solid tumor and hematologic settings), as well as other conditions that are mediated by Pim kinase signaling.

[0009] In addition to the malignant cells detailed above, PIM kinases are also expressed in hematopoietically-derived cell lines and hematopoietically-derived primary cells including cells of the immune system such as B cells, T cells, monocytes, macrophages, eosinophils, basophils, and dendritic cells. Expression of PIM kinases is induced by cytokines which utilize Jak/Stat signaling, such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-15, GM-CSF, IFN α , IFN γ , erythropoietin, thrombopoietin, and prolactin, and the generation, differentiation, maintenance and activation of hematopoietically-derived cells is dependent on these cytokines. Moreover, PIM proteins have been shown to be required for the efficient proliferation of peripheral T cells mediated by T-cell receptor and IL-2 signaling (Mikkers, et al., *Mol. Cell Biol.*, 2004, 6104). Although the exact mechanism of action of PIM kinases in an immunological setting has yet to be fully defined, they have been reported to phosphorylate a number of substrates involved in cellular proliferation, differentiation, and survival (Bullock et al., *J. Biol. Chem.*, 2005 280:41675; Chen et al., *PNAS* 2002 99:2175; Dautry et al., *J. Biol. Chem.* 1998 263:17615).

[0010] Chronic and acute inflammatory and autoimmune diseases are associated with the overproduction of pro-inflammatory cytokines and activation of immune cells against the body's own tissues. However, many of these diseases are not adequately treated by current therapies and/or these therapies have significant side effects/risks.

[0011] A particular example of an autoimmune disease is multiple sclerosis (MS). MS is a progressive central nervous system (CNS) inflammatory autoimmune disease wherein the immune system mounts responses against CNS components. The resulting damage to axons and nerves leads to progressive neurological impairment and significant disability. MS affects over 2.5 million people worldwide (www.nationalmssociety.org);

however many current therapies are only moderately effective and have questionable risk factors

[0012] A need therefore remains for compounds and methods for treating autoimmune and inflammatory diseases.

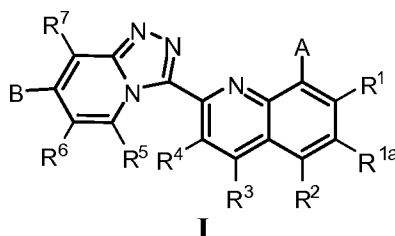
[0013] International patent application, publication number WO 2004/058769 discloses, *inter alia*, certain 3-aryl and 3-N-arylamino-substituted [1,2,4]triazolo[4,3-b]pyridazines purported to inhibit several protein kinases, including PIM-1.

[0014] International patent application, publication number WO 2008/022164 discloses phenyl- and pyridyl-substituted pyrazines and pyridines as PIM-2 inhibitors said to be useful in the treatment of cancer and inflammation.

[0015] International patent application, publication number WO 2008/106692, published 4 September 2008 after the first priority date for the present invention, discloses carboxamide-substituted pyridines and 2-oxopyrimidines which are inhibitors of PIM-1, PIM-2 and PIM-3.

[0016] It has now been found that certain [1,2,4]triazole[4,3-a]pyridine compounds bearing a quinolinyl group at the 3 position of the triazolopyridine ring are inhibitors of PIM kinases, in particular PIM-1, PIM-2 and/or PIM-3 kinases, which are useful for treating diseases such as cancers and inflammatory diseases. In addition, compounds of the invention may be useful for treating immune cell-associated diseases and disorders, such as inflammatory and autoimmune diseases.

[0017] Accordingly, provided is a compound of general Formula I:



[0018] or a pharmaceutically acceptable salt thereof, wherein:

[0019] A is OR¹⁰ or NR¹¹R¹²;

[0020] B is H, F, Cl, OR^a, (1-6C alkyl)NR^bR^c, (1-6C alkyl)OH, CH(OH)CH₂OH, or (1-4C alkyl);

[0021] R¹ is H, F, Cl, Br, Me, cyclopropyl or CN;

[0022] R^{1a}, R², R³ and R⁴ are independently H, F, Cl, Br, Me or CN;

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

- [0024] R^6 is H, F, Me, Br, CN, cyclopropyl, phenyl, MeO- or MeOCH₂CH₂O-;
- [0025] R^{10} is H, hetCyc¹, -(1-3C alkyl)hetCyc^{1a}, hetCyc², (CR¹⁷R¹⁸)_p(CR¹³R¹⁴)CH₂NR¹⁵R¹⁶, -(CR¹⁷R¹⁸)_p(CR¹³R¹⁴)CH₂OH, (1-6C alkyl), hetAr¹, (1-3C alkyl)hetAr^{1a}, or (3-7C)cycloalkyl substituted with NH₂, NH(1-6C alkyl) or N(1-6C alkyl)₂;
- [0026] R^{11} is H or (1-6C)alkyl;
- [0027] R^{12} is hetCyc³, (1-6C alkyl)NR¹⁵R¹⁶, C(O)(1-6C alkyl)NR¹⁵R¹⁶, (1-6C alkyl)NHC(O)O(1-6C alkyl), or (4-7C)cycloalkyl optionally substituted with OH, NH₂, NH(1-6C alkyl) or N(1-6C alkyl)₂;
- [0028] R^{13} is H, (1-6C)alkyl, F or OH, and
- [0029] R^{14} is H, (1-6C)alkyl or F, or
- [0030] R^{13} and R^{14} together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;
- [0031] each R^{15} , R^{16} , R^{17} and R^{18} is independently H or (1-6C)alkyl,
- [0032] or each R^{15} , R^{17} and R^{18} is independently H or (1-6C)alkyl and R^{16} is H, (1-6C)alkyl, C(=O)CH₂F, CH₂CHF₂ or CH₂CF₃;
- [0033] or NR¹⁵R¹⁶ forms a 5-6 membered heterocyclic ring having a first ring heteroatom which is N and optionally having a second ring heteroatom selected from N and O;
- [0034] hetCyc¹, hetCyc^{1a}, and hetCyc³ are independently a 4-7 membered heterocycle having a ring nitrogen atom and optionally substituted with one or more R⁹ groups, or
- [0035] hetCyc¹ and hetCyc³ are independently a 4-7 membered heterocycle having a ring nitrogen atom and optionally substituted with one or more R⁹ groups, and hetCyc^{1a} is selected from a morpholinyl and 4-7 membered azacyclic ring optionally substituted with one or more R⁹ groups;
- [0036] each R⁹ is independently selected from halogen, (1-6C)alkyl, cyclopropylmethyl, benzyl, NR^fR^g, -(1-6C alkyl)NR^hRⁱ, OR^j, (1-6C alkyl)OR^k, (1-6C)fluoroalkyl, C(O)NR^mRⁿ, (1-6C alkyl)C(O)NR^pR^q, and C(O)O(1-6C alkyl);
- [0037] hetCyc² is an 8-membered bridged heterocycle having a ring nitrogen atom;
- [0038] hetAr¹ and hetAr^{1a} are independently a 5 or 6 membered heteroaryl having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from F, Cl, Br, Me, cyclopropyl, CN, NH₂, NH(1-6C alkyl) and N(1-6C alkyl)₂;
- [0039] R^a is H, (1-6C alkyl), -(1-6C alkyl)-O-(1-6C alkyl) or -(1-6C alkyl)-O-(3-6C cycloalkyl);

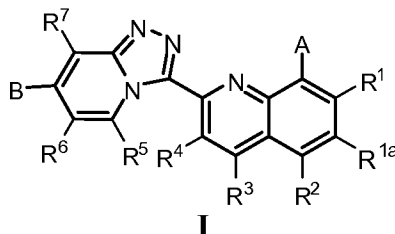
[0040] each R^b , R^f , R^g , R^h , R^i , R^k , R^m , R^p and R^q is independently selected from H and (1-6C alkyl);

[0041] R^j is H, (1-6C alkyl) or cyclopropyl;

[0042] R^n is H, (1-6C alkyl), -O(1-6C alkyl) or -O(3-6C cycloalkyl); and

[0043] p is 0, 1 or 2.

[0044] Also provided is a compound of general Formula I:



[0045] or a pharmaceutically acceptable salt thereof, wherein:

[0046] A is OR^{10} or $NR^{11}R^{12}$;

[0047] B is H, F, OR^a , (1-6C alkyl) NR^bR^c , (1-6C alkyl)OH, $CH(OH)CH_2OH$, or (1-4C alkyl);

[0048] R^1 is H, F, Cl, Br, Me, cyclopropyl or CN;

[0049] R^{1a} , R^2 , R^3 and R^4 are independently H, F, Cl, Br, Me or CN;

[0050] R^5 and R^7 are independently H, F, Me or CN;

[0051] R^6 is H, F, Me, Br, CN, cyclopropyl or phenyl;

[0052] R^{10} is H, $hetCyc^1$, $-(1-3C\ alkyl)hetCyc^{1a}$, $hetCyc^2$, $(CR^{17}R^{18})_p(CR^{13}R^{14})CH_2NR^{15}R^{16}$, $-(CR^{17}R^{18})_p(CR^{13}R^{14})CH_2OH$, (1-6C alkyl), $hetAr^1$, (1-3C alkyl) $hetAr^{1a}$, or (3-7C)cycloalkyl substituted with NH_2 , $NH(1-6C\ alkyl)$ or $N(1-6C\ alkyl)_2$;

[0053] R^{11} is H or (1-6C)alkyl;

[0054] R^{12} is $hetCyc^3$, (1-6C alkyl) $NR^{15}R^{16}$, $C(O)(1-6C\ alkyl)NR^{15}R^{16}$, (1-6C alkyl) $NHC(O)O(1-6C\ alkyl)$, or (4-7C)cycloalkyl optionally substituted with OH, NH_2 , $NH(1-6C\ alkyl)$ or $N(1-6C\ alkyl)_2$;

[0055] R^{13} is H, (1-6C)alkyl, F or OH, and

[0056] R^{14} is H, (1-6C)alkyl or F, or

[0057] R^{13} and R^{14} together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

[0058] each R^{15} , R^{16} , R^{17} and R^{18} is independently H or (1-6C)alkyl,

[0059] or $\text{NR}^{15}\text{R}^{16}$ forms a 5-6 membered heterocyclic ring having a first ring heteroatom which is N and optionally having a second ring heteroatom selected from N and O;

[0060] hetCyc^1 , hetCyc^{1a} , and hetCyc^3 are independently a 4-7 membered heterocycle having a ring nitrogen atom and optionally substituted with one or more R^9 groups;

[0061] each R^9 is independently selected from halogen, (1-6C)alkyl, cyclopropylmethyl, benzyl, NR^fR^g , $-(1-6\text{C alkyl})\text{NR}^h\text{R}^i$, OR^j , $(1-6\text{C alkyl})\text{OR}^k$, (1-6C)fluoroalkyl, $\text{C}(\text{O})\text{NR}^m\text{R}^n$, $(1-6\text{C alkyl})\text{C}(\text{O})\text{NR}^p\text{R}^q$, and $\text{C}(\text{O})\text{O}(1-6\text{C alkyl})$;

[0062] hetCyc^2 is an 8-membered bridged heterocycle having a ring nitrogen atom;

[0063] hetAr^1 and hetAr^{1a} are independently a 5 or 6 membered heteroaryl having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from F, Cl, Br, Me, cyclopropyl, CN, NH_2 , $\text{NH}(1-6\text{C alkyl})$ and $\text{N}(1-6\text{C alkyl})_2$;

[0064] R^a is H, (1-6C alkyl), $-(1-6\text{C alkyl})\text{-O-(1-6C alkyl)}$ or $-(1-6\text{C alkyl})\text{-O-(3-6C cycloalkyl)}$;

[0065] each R^b , R^f , R^g , R^h , R^i , R^k , R^m , R^p and R^q is independently selected from H and (1-6C alkyl);

[0066] R^j is H, (1-6C alkyl) or cyclopropyl;

[0067] R^n is H, (1-6C alkyl), $-\text{O}(1-6\text{C alkyl})$ or $-\text{O}(3-6\text{C cycloalkyl})$; and

[0068] p is 0, 1 or 2.

[0069] In certain embodiments, B is selected from any of the values described above, other than (1-4C alkyl).

[0070] 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.

[0071] In certain embodiments, R^1 is H, F or Cl. In certain embodiments, R^1 is H. In certain embodiments, R^1 is F. In certain embodiments, R^1 is Br.

[0072] In certain embodiments, R^{1a} is H or F. In certain embodiments, R^{1a} is H.

[0073] In certain embodiments, R^2 is H.

[0074] In certain embodiments, R^3 is H.

- [0075] In certain embodiments, R⁴ is H.
- [0076] In certain embodiments, R⁵ is H.
- [0077] In certain embodiments, R⁶ is H, F, or Br.
- [0078] In certain embodiments, R⁶ is CN or Me.
- [0079] In certain embodiments, R⁶ is phenyl or cyclopropyl.
- [0080] In certain embodiments, R⁶ is MeO- or MeOCH₂CH₂O-.
- [0081] In certain embodiments, R⁶ is H.
- [0082] In certain embodiments, R⁷ is H.
- [0083] In certain embodiments, each of R², R³, R⁴, R⁵ and R⁷ is H.
- [0084] In certain embodiments, each of R¹, R^{1a}, R², R³, R⁴, R⁵, R⁶ and R⁷ is H.
- [0085] In certain embodiments, A is OR¹⁰.
- [0086] In certain embodiments, A is OR¹⁰ where R¹⁰ is represented by the formula hetCyc¹ or (1-3C alkyl)hetCyc^{1a}. Particular examples of hetCyc¹ and hetCyc^{1a} rings include piperidiny, pyrrolidiny and azepany rings. In certain embodiments, hetCyc¹ and hetCyc^{1a} are substituted with one or more R⁹ groups.
- [0087] Examples of R⁹ groups when represented by halogen include F, Cl and Br.
- [0088] In certain embodiments, R⁹ is cyclopropylmethyl.
- [0089] In certain embodiments, R⁹ is benzyl.
- [0090] Examples of R⁹ groups represented by the formula (1-6C)alkyl include methyl, ethyl, propyl and isopropyl.
- [0091] Examples of R⁹ groups represented by the formula NR^fR^g include groups where R^f is H or Me and R^g is H, methyl, ethyl, propyl, isopropyl, butyl, or isobutyl. Particular values of R⁹ when represented by NR^fR^g include NH₂ and NHMe.
- [0092] Examples of R⁹ groups represented by the formula -(1-6C alkyl)NR^hRⁱ, include groups where R^h is H and Rⁱ is H or (1-6C)alkyl. Particular values of R⁹ when represented by -(1-6C alkyl)NR^hRⁱ include CH₂NR^hRⁱ, for example CH₂NH₂ and CH₂NHMe.
- [0093] Examples of R⁹ groups having the formula OR^j include groups where R^j is H, (1-6C) alkyl [for example methyl, ethyl, or isopropyl] or cyclopropyl. Particular examples of R⁹ when represented by OR^j include OH, OMe and -O-cyclopropyl.
- [0094] Examples of R⁹ groups represented by the formula (1-6C alkyl)OR^k include groups where R^k is H or Me. Particular values of such substituents include CH₂OH, CH₂CH₂OH and CH₂OMe.

[0095] An example of R⁹ groups represented by the formula (1-6C)fluoroalkyl includes CH₂CH₂F.

[0096] Examples of R⁹ groups having the formula C(O)NR^mRⁿ include groups where R^m is H or (1-6C) alkyl (for example H or methyl). In certain embodiments, Rⁿ is H, (1-6C alkyl) or O-(1-6C alkyl), (for example H, methyl or OMe. Particular values of R⁹ include C(O)NH₂ and C(O)NMe(OMe).

[0097] Examples of R⁹ groups having the formula (1-6C alkyl)C(O)NR^pR^q include groups where both R^p and R^q are hydrogen. In other embodiments, one of R^p and R^q is hydrogen and the other is (1-6C alkyl). In other embodiments, both R^p and R^q are independently selected from (1-6C alkyl), for example methyl or ethyl. Particular values of R⁹ include CH₂C(=O)NH₂, CH₂CH₂C(=O)NH₂, CH₂C(=O)NHMe and CH₂C(=O)NMe₂.

[0098] Examples of R⁹ groups having the formula C(O)O(1-6C alkyl) include CO₂Me and CO₂C(CH₃)₃.

[0099] In particular embodiments, hetCyc¹ and hetCyc^{1a} are unsubstituted or substituted with one or more R⁹ groups independently selected from F, (1-6C)alkyl, cyclopropylmethyl, benzyl, C(O)O(1-6C)alkyl, (1-6C alkyl)OR^k, C(O)NR^mRⁿ, (1-6C alkyl)C(O)NR^pR^q, OR^j and (1-6C)fluoroalkyl.

[00100] In particular embodiments, hetCyc¹ and hetCyc^{1a} are unsubstituted or substituted with one or more R⁹ groups independently selected from F, (1-6C)alkyl, cyclopropylmethyl, benzyl, C(O)O(1-6C)alkyl, (1-6C alkyl)OR^k, C(O)NR^mRⁿ, (1-6C alkyl)C(O)NR^pR^q and OR^j.

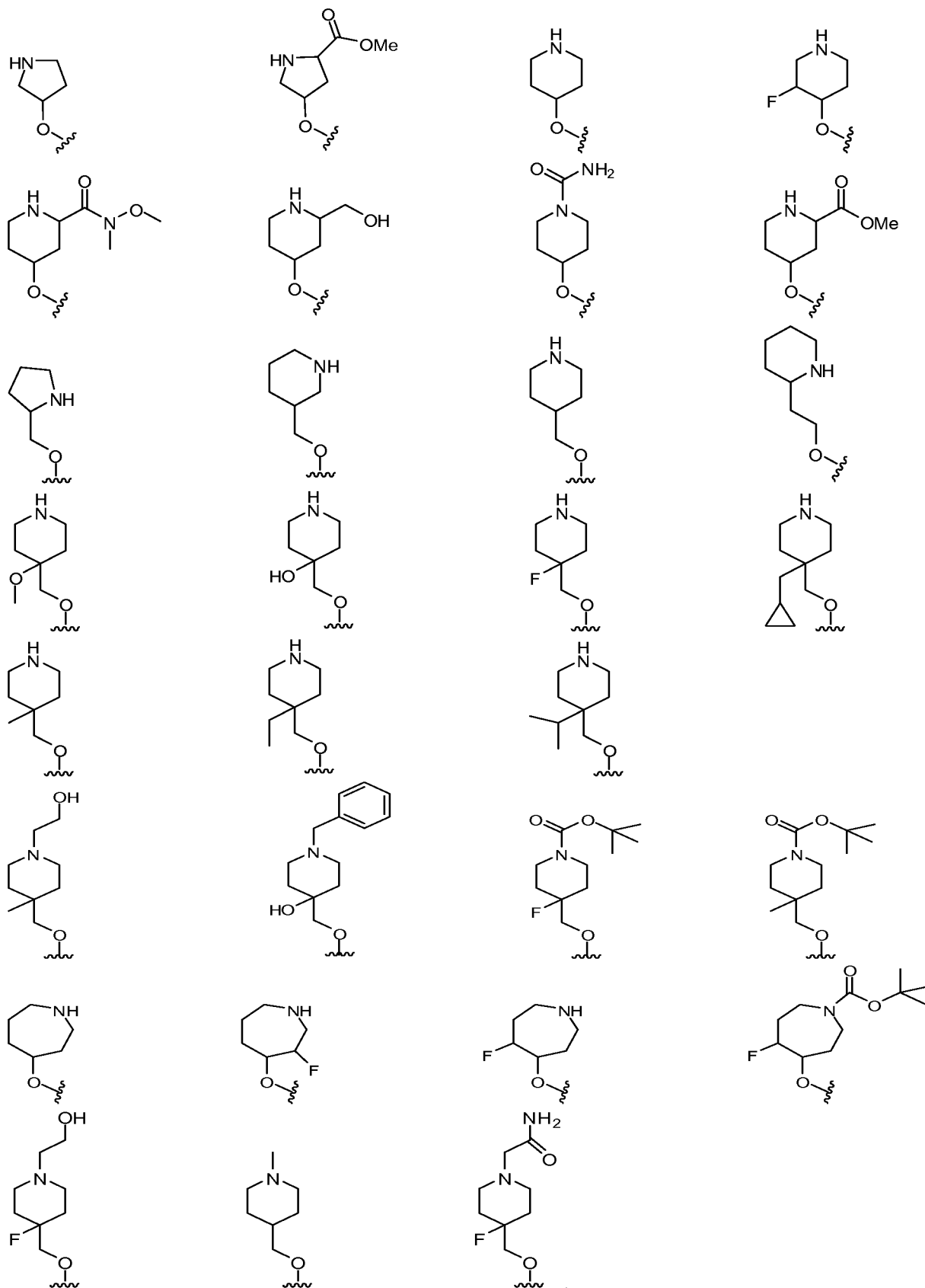
[00101] In certain embodiments, hetCyc¹ and hetCyc^{1a} are optionally substituted with one or more substituents independently selected from F, methyl, ethyl, isopropyl, CO₂Me, CO₂C(CH₃)₃, C(O)NH₂, C(O)N(Me)OMe, CH₂C(=O)NH₂, cyclopropylmethyl, benzyl, CH₂OH, CH₂CH₂OH, OH, OMe, and CH₂CH₂F.

[00102] In particular embodiments, hetCyc¹ and hetCyc^{1a} are optionally substituted with one or more substituents independently selected from F, methyl, ethyl, isopropyl, CO₂Me, CO₂C(CH₃)₃, C(O)NH₂, C(O)N(Me)OMe, CH₂C(=O)NH₂, cyclopropylmethyl, benzyl, CH₂OH, CH₂CH₂OH, OH, and OMe.

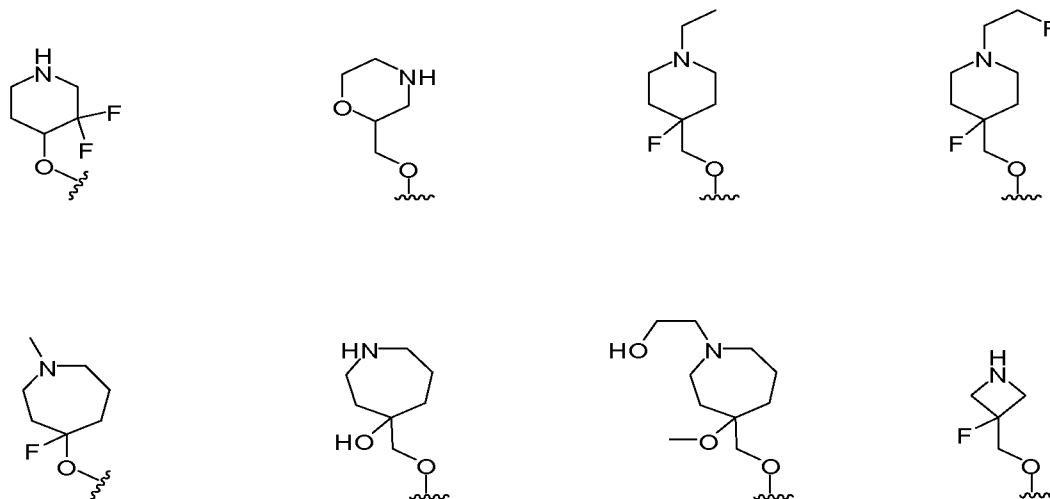
[00103] In certain embodiments, each hetCyc¹ and hetCyc^{1a} is independently and optionally substituted with one or two R⁹ groups.

[00104] In another embodiment, A is OR¹⁰ where R¹⁰ is represented by the formula (1-3C alkyl)hetCyc^{1a} and hetCyc^{1a} is morpholinyl.

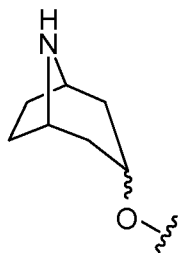
[00105] Particular embodiments of OR¹⁰ when R¹⁰ is hetCyc¹ or (1-3C alkyl)hetCyc^{1a} include the structures:



[00106] Additional examples of OR^{10} when R^{10} is hetCyc¹ or (1-3C alkyl)hetCyc^{1a} include the structures:

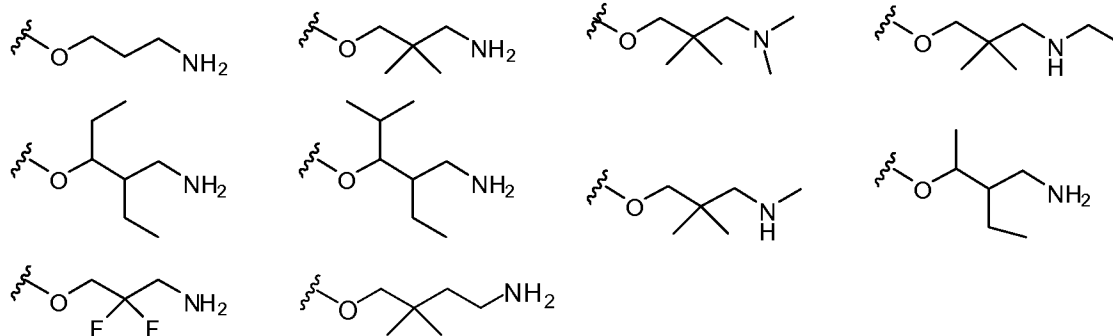


[00107] In certain embodiments, A is OR^{10} where R^{10} is hetCyc². Particular examples of hetCyc² include bridged heterocyclic ring systems such as 8-azabicyclo[3.2.1]octane ring systems. A particular value of OR^{10} when represented by $-O\text{-hetCyc}^2$ includes the structure:

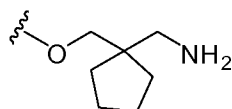


[00108] In certain embodiments, A is OR^{10} where R^{10} is represented by the formula $(CR^{17}R^{18})_p(CR^{13}R^{14})CH_2NR^{15}R^{16}$. In certain embodiments, p is 0. In other embodiments, p is 1 or 2. In certain embodiments, R^{17} and R^{18} are both H. In certain embodiments, R^{17} and R^{18} are both independently selected from a (1-6C alkyl) group, for example methyl, ethyl, propyl and isopropyl. In certain embodiments, one of R^{17} and R^{18} is H and the other is (1-6C alkyl). In certain embodiments, R^{13} and R^{14} are each H. In certain embodiments, R^{13} and R^{14} are each F. In other embodiments, R^{13} and R^{14} are independently H or (1-6C) alkyl, for example methyl, ethyl, propyl or isopropyl. In other embodiments, R^{13} and R^{14} together with the carbon atom to which they are attached form a cyclopropyl ring. In certain embodiments, R^{15} and R^{16} are each H. In other embodiments, R^{15} and R^{16} are independently H or (1-6C) alkyl, for example methyl, ethyl, propyl or isopropyl. In certain embodiments, R^{17} is H. In other embodiments, R^{17} is (1-6C alkyl), for example methyl, ethyl, propyl or isopropyl. Particular embodiments of OR^{10} when represented by $-O-(CR^{17}R^{18})_p(CR^{13}R^{14})CH_2NR^{15}R^{16}$ include the structures:

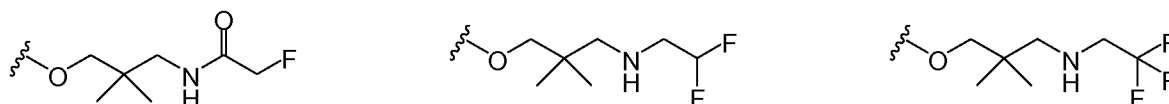
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[00109] In certain embodiments, A is OR^{10} where R^{10} is represented by the formula $(CR^{17}R^{18})_p(CR^{13}R^{14})CH_2NR^{15}R^{16}$ and R^{13} and R^{14} together with the carbon atom to which they are attached form a cyclopentyl ring. A particular example is the structure:



[00110] In certain embodiments, A is OR^{10} where R^{10} is represented by the formula $(CR^{17}R^{18})_p(CR^{13}R^{14})CH_2NR^{15}R^{16}$, where each R^{15} , R^{17} and R^{18} is independently H or (1-6C)alkyl and R^{16} is H, (1-6C)alkyl, $C(=O)CH_2F$, CH_2CHF_2 or CH_2CF_3 . In certain embodiments, R^{15} , R^{17} and R^{18} are H and R^{16} is $C(=O)CH_2F$, CH_2CHF_2 or CH_2CF_3 . Particular examples include the structures:



[00111] In certain embodiments, A is OR^{10} where R^{10} is represented by the formula $(CR^{17}R^{18})_p(CR^{13}R^{14})CH_2OH$. In certain embodiments, p is 0. In other embodiments, p is 1 or 2. In certain embodiments, R^{17} and R^{18} are both hydrogen. In certain embodiments, R^{17} and R^{18} are both independently selected from (1-6C alkyl), for example independently selected from methyl, ethyl and propyl. In certain embodiments, one of R^{17} and R^{18} is hydrogen and the other is selected from (1-6C alkyl). In certain embodiments, R^{13} and R^{14} are each H. In certain embodiments, R^{13} and R^{14} are each independently selected from a (1-6C)alkyl group, such as methyl, ethyl, propyl or isopropyl. In other embodiments, R^{13} is OH, and R^{14} is H. In other embodiments, R^{13} and R^{14} together with the atom to which they are attached form a 3-6 membered carbocycle, for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring. Particular embodiments of OR^{10} when represented by $-O-(CR^{17}R^{18})_p(CR^{13}R^{14})CH_2OH$ include the structures:

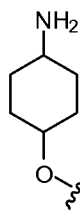




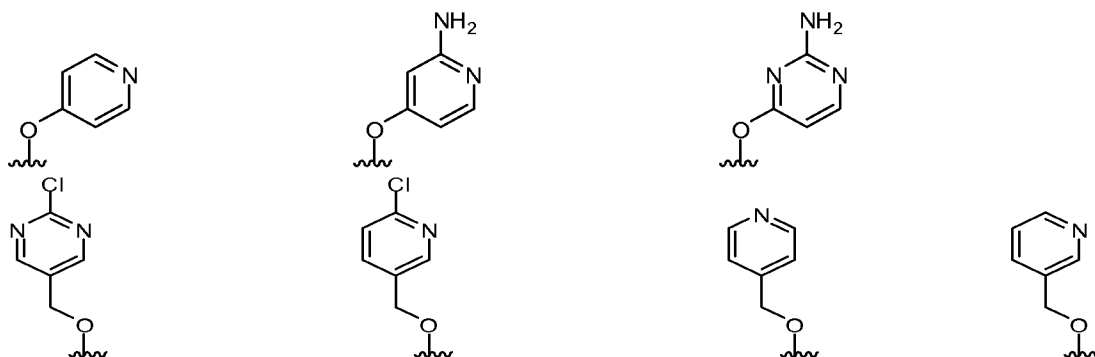
[00112] In certain embodiments, A is OR^{10} where R^{10} is (1-6C alkyl). Particular examples of OR^{10} include the structures:



[00113] In certain embodiments, A is OR^{10} where R^{10} is (3-7C)cycloalkyl substituted with a substituent selected from NH_2 , $NH(1-6C\text{ alkyl})$ or $N(1-6C\text{ alkyl})_2$, for example NH_2 , $NHMe$ or NMe_2 . A particular value of OR^{10} when R^{10} is (3-6C)cycloalkyl includes the structure:



[00114] In certain embodiments, A is OR^{10} where R^{10} is $hetAr^1$ or (1-3Calkyl) $hetAr^{1a}$. Examples of $hetAr^1$ and $hetAr^{1a}$ include pyridyl and pyrimidyl rings optionally substituted with Cl or NH_2 . Particular values of OR^{10} when R^{10} is $hetAr^1$ or (1-3Calkyl) $hetAr^{1a}$ include the structures:

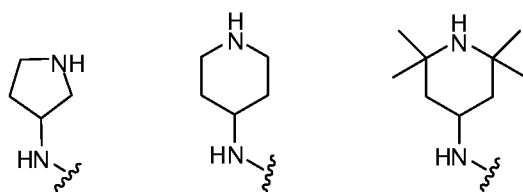


[00115] In certain embodiments, A is OH.

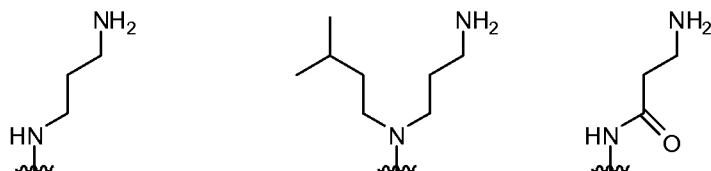
[00116] In certain embodiments, A is $NR^{11}R^{12}$.

[00117] In certain embodiments, A is $NR^{11}R^{12}$, wherein R^{12} is $hetCyc^3$ optionally substituted with one or more R^9 groups described hereinabove. Particular examples of $hetCyc^3$ include piperidinyl and pyrrolidinyl rings. In certain embodiments, $hetCyc^3$ is substituted with one or more R^9 groups independently selected from (1-6C) alkyl. In certain embodiments, R^{11} is H. Particular examples of $NR^{11}R^{12}$ when R^{12} is $hetCyc^3$ include the structures:

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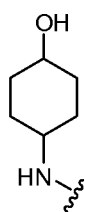
[00118] In certain embodiments, A is $\text{NR}^{11}\text{R}^{12}$ and R^{12} is (1-6C alkyl) $\text{NR}^{15}\text{R}^{16}$. In certain embodiments, R^{11} is H. In certain embodiments, R^{15} and R^{16} are each H. In certain embodiments, R^{15} is H and R^{16} is (1-6C)alkyl, for example methyl, ethyl, propyl or isopropyl. In certain embodiments, $\text{NR}^{15}\text{R}^{16}$ forms a 5-6 membered heterocyclic ring having a first ring heteroatom which is N and optionally having a second ring heteroatom selected from N and O. Examples of heterocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl. Particular embodiments of $\text{NR}^{11}\text{R}^{12}$ include the structures:



[00119] In certain embodiments, A is $\text{NR}^{11}\text{R}^{12}$, wherein R^{12} is $\text{C}(\text{O})(1-6\text{C alkyl})\text{NR}^{15}\text{R}^{16}$. In certain embodiments, R^{11} is H. In certain embodiments, R^{15} and R^{16} are each H. In certain embodiments, R^{15} is H and R^{16} is (1-6C)alkyl, for example methyl, ethyl, propyl or isopropyl. In certain embodiments, $\text{NR}^{15}\text{R}^{16}$ forms a 5-6 membered heterocyclic ring having a first ring heteroatom which is N and optionally having a second ring heteroatom selected from N and O. Examples of heterocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl. A particular value of $\text{NR}^{11}\text{R}^{12}$ is $\text{NHC}(\text{O})\text{CH}_2\text{CH}_2\text{NH}_2$.

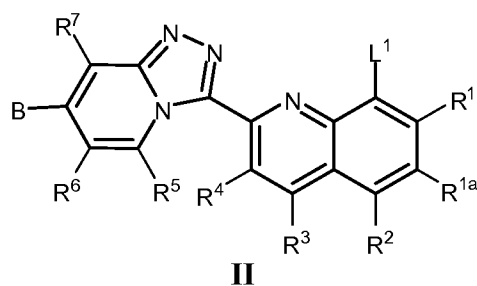
[00120] In certain embodiments, A is $\text{NR}^{11}\text{R}^{12}$, wherein R^{12} is (1-6 C alkyl) $\text{NHC}(\text{O})\text{O}(1-6\text{C alkyl})$, for example (1-6 C alkyl) $\text{NHC}(\text{O})\text{OC}(\text{CH}_3)_3$. In certain embodiments, R^{11} is H. A particular value of $\text{NR}^{11}\text{R}^{12}$ is $(\text{CH}_2)_3\text{NHCO}_2\text{C}(\text{CH}_3)_3$.

[00121] In certain embodiments, A is $\text{NR}^{11}\text{R}^{12}$, wherein R^{12} is (4-7C)cycloalkyl substituted with a substituent selected from OH, NH_2 , $\text{NH}(1-6\text{C alkyl})$ or $\text{N}(1-6\text{C alkyl})_2$. In certain embodiments, R^{11} is H. A particular example of A is the structure:



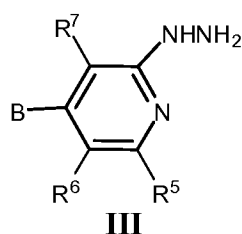
- [00122] In certain embodiments, B is H.
- [00123] In certain embodiments, B is F.
- [00124] In certain embodiments, B is OR^a.
- [00125] Examples of OR^a when R^a is represented by (1-6C)alkyl include OMe, OEt and O-(isobutyl). A particular value of B when represented by OR^a is OMe.
- [00126] Examples of OR^a when R^a is represented by -(1-6C alkyl)-O-(1-6C alkyl) include -OCH₂CH₂OMe and -OCH₂CH₂CH₂OMe. A particular value of B when represented by OR^a is -OCH₂CH₂OMe.
- [00127] In certain embodiments, B is (1-6C alkyl)NR^bR^c. In certain embodiments, R^b is H and R^c is H or (1-6C)alkyl. Particular values of B include groups having the formula CH₂NR^bR^c, for example CH₂NHEt and CH₂NH₂.
- [00128] In certain embodiments, B is (1-6C alkyl)OH. A particular value of B is CH₂OH.
- [00129] In certain embodiments, B is CH(OH)CH₂OH.
- [00130] In certain embodiments, B is (1-4C alkyl). A particular example is methyl.
- [00131] 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.
- [00132] 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.
- [00133] 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.
- [00134] Examples of salts of Formula I include acid addition salts, including salts of inorganic and organic acids. Particular mention is made of hydrochloride and trifluoroacetate salts of Formula I.
- [00135] 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:
- [00136] (a) for a compound of Formula I wherein A is NR¹¹R¹², coupling a corresponding compound having the formula II

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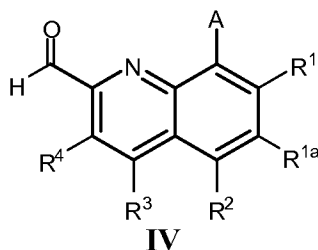


[00137] wherein L^1 represents a leaving atom or group, with a compound having the formula $HNR^{11}R^{12}$, using a palladium (II) catalyst and a ligand in the presence of a base; or

[00138] (b) reacting a compound of Formula III

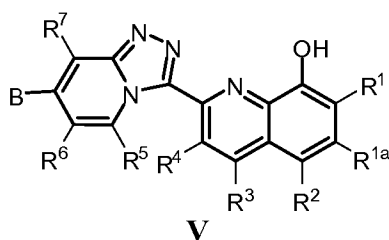


[00139] with a compound having the Formula IV



[00140] in the presence of an organo hypervalent iodine reagent; or

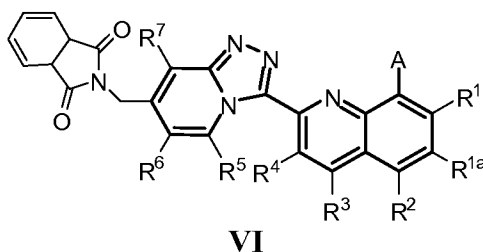
[00141] (c) for a compound of Formula I wherein A is OR^{10} , coupling a corresponding compound having the Formula V



[00142] with a compound having the formula $HO-R^{10}$ in the presence of a coupling agent and triphenylphosphine in a suitable solvent; or

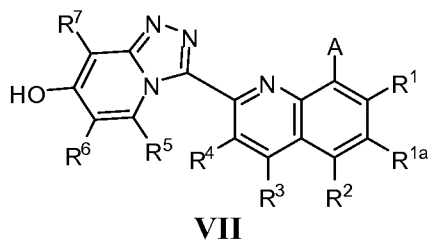
[00143] (d) for a compound of Formula I wherein B is $(CH_2)NR^bR^c$, reacting a corresponding compound having the Formula VI

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[00144] with hydrazine; or

[00145] (e) for a compound of Formula I where B is OR^a, reacting a corresponding compound having the Formula VII



[00146] with a compound of the formula R^a-L², wherein L² represents a leaving atom or group, in the presence of a base; and

[00147] removing any protecting group or groups and, if desired, forming a salt.

[00148] 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 hydrocarbylsulfonyloxy 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 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. Alternatively, the reaction can be performed in the absence of a solvent. The coupling of a compound of formula (II) with HNR¹¹R¹² can be conveniently performed at a temperature between 0 °C and reflux, and more particularly at reflux, for example at 100 °C.

[00149] Referring to method (b), the organo hypervalent iodine reagent refers to any hypervalent iodine reagent suitable for forming heterocyclic rings. Examples include iodobenzene diacetate (IBD) and [hydroxy(tosyloxy)iodo]benzene (HTIB), which can be prepared by treating IBD with *p*-toluenesulfonic acid monohydrate in acetonitrile. Suitable solvent systems when using IBD include methanolic potassium hydroxide. Suitable solvent

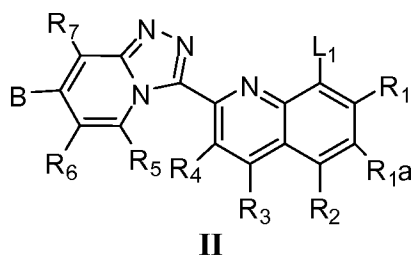
systems when using HTIB include neutral solvents, for example acetonitrile or dioxane. The reaction can be performed at a temperature ranging from 80 to 110 °C.

[00150] 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.

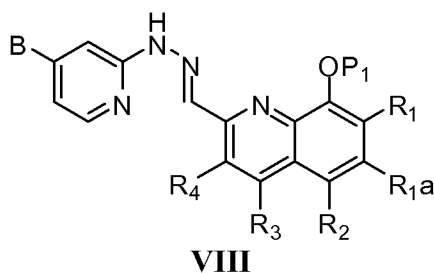
[00151] Referring to method (d), the reaction is conveniently performed at ambient temperature. Suitable solvents include alcohols such as methanol.

[00152] Referring to method (e), the leaving atom L² may be, for example a halogen atom such as Br, Cl or I. Alternatively, L² 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.

[00153] A compound of Formula II

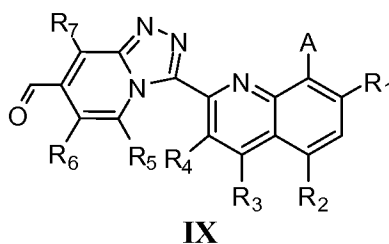


[00154] can be prepared by cyclizing a corresponding compound having the formula VIII



[00155] where P¹ is an alcohol protecting group, in the presence of an organo hypervalent iodine reagent as described above, followed by deprotection of the alcohol group and conversion of the alcohol group to an alkylsulfonyloxy group, such as a mesylate or a tosylate group.

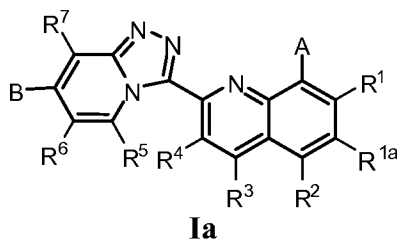
[00156] A compound of Formula VI can be prepared by reducing a corresponding aldehyde having the formula IX



[00157] to the corresponding alcohol, followed by reacting the alcohol with isoindoline-1,3-dione in the presence of triphenylphosphine.

[00158] The compounds of the formulas (II), (V), (VI), (VIII) and (IX) are believed to be novel and are provided as further aspects of the invention.

[00159] The compounds of Formula I include compounds of Formula Ia



[00160] and pharmaceutically acceptable salts thereof, wherein:

[00161] A is OR¹⁰;

[00162] B is H, -CH₂NH₂, -OMe, -OCH₂CH₂OMe, F, Cl or Me;

[00163] R¹ is H, F, Cl, Br, Me, cyclopropyl or CN;

[00164] R^{1a}, R², R³ and R⁴ are independently H, F, Cl, Br, Me or CN;

[00165] R⁵ and R⁷ are independently H, F, Me or CN;

[00166] R⁶ is H, F, Me, Br, CN, cyclopropyl, phenyl, -OMe, or -OCH₂CH₂OMe;

[00167] R¹⁰ is hetCyc¹, -(1-3C alkyl)hetCyc^{1a} or hetCyc²;

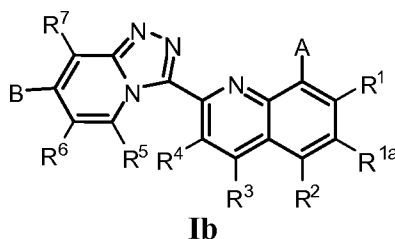
[00168] hetCyc¹ is a 4-7 membered heterocycle having a ring nitrogen atom and optionally substituted with one or more R⁹ groups;

[00169] hetCyc^{1a} is selected from a morpholinyl and 4-7 membered azacyclic ring optionally substituted with one or more R⁹ groups;

[00170] each R⁹ is independently selected from halogen, (1-6C)alkyl, cyclopropylmethyl, OR^j, (1-6C alkyl)OR^k, (1-6C)fluoroalkyl, C(O)NR^mRⁿ, (1-6C alkyl)C(O)NR^pR^q, and C(O)O(1-6C alkyl);

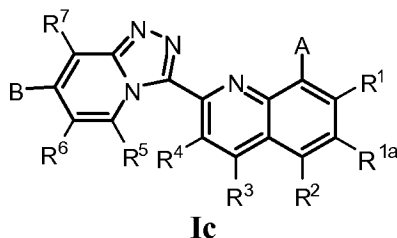
[00171] hetCyc² is an 8-membered bridged heterocycle having a ring nitrogen atom;

- [00172] each R^k , R^m , R^p and R^q is independently selected from H and (1-6C alkyl);
- [00173] R^j is H, (1-6C alkyl) or cyclopropyl;
- [00174] R^n is H, (1-6C alkyl), -O(1-6C alkyl) or -O(3-6C cycloalkyl); and
- [00175] p is 0, 1 or 2.
- [00176] In certain embodiments of Formula **Ia**, each of R^1 , R^2 , R^3 , R^5 and R^7 is hydrogen.
- [00177] In certain embodiments of Formula **Ia**, B is hydrogen.
- [00178] In certain embodiments of Formula **Ia**, R^{10} is hetCyc¹ or -(1-3C alkyl)hetCyc^{1a}.
- [00179] In certain embodiments of Formula **Ia**, hetCyc¹ and -(1-3C alkyl)hetCyc^{1a} are optionally substituted with one or two R^9 groups independently selected from Me, Et, isopropyl, cyclopropylmethyl, F, OH, OMe, CH₂OH, CH₂CH₂OH, CH₂CH₂F, CH₂OMe, C(=O)OMe, C(=O)NH₂ and CH₂C(=O)NH₂.
- [00180] The compounds of Formula **I** include compounds of Formula **Ib**

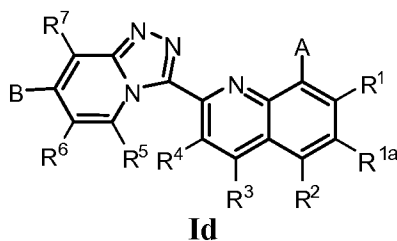


- [00181] and pharmaceutically acceptable salts thereof, wherein:
- [00182] A is OR¹⁰;
- [00183] B is H, -CH₂NH₂, -OMe, -OCH₂CH₂OMe, F, Cl or Me;
- [00184] R¹ is H, F, Cl, Br, Me, cyclopropyl or CN;
- [00185] R^{1a}, R², R³ and R⁴ are independently H, F, Cl, Br, Me or CN;
- [00186] R⁵ and R⁷ are independently H, F, Me or CN;
- [00187] R⁶ is H, F, Me, Br, CN, cyclopropyl or phenyl;
- [00188] R¹⁰ is H, (CR¹⁷R¹⁸)_p(CR¹³R¹⁴)CH₂NR¹⁵R¹⁶, -(CR¹⁷R¹⁸)_p(CR¹³R¹⁴)CH₂OH, (1-6C alkyl), or a (3-7C)cycloalkyl ring substituted with NH₂, NH(1-6C alkyl) or N(1-6C alkyl)₂;
- [00189] R¹³ is H, (1-6C)alkyl, F or OH, and
- [00190] R¹⁴ is H, (1-6C)alkyl or F, or
- [00191] R¹³ and R¹⁴ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

- [00192] each R¹⁵, R¹⁷ and R¹⁸ is independently H or (1-6C)alkyl;
 [00193] R¹⁶ is H, (1-6C)alkyl, C(=O)CH₂F, CH₂CHF₂ or CH₂CF₃; and
 [00194] p is 0, 1 or 2.
 [00195] In certain embodiments of Formula **Ib**, each of R¹, R², R³, R⁵ and R⁷ is hydrogen.
 [00196] In certain embodiments of Formula **Ib**, B is hydrogen.
 [00197] The compounds of Formula **I** include compounds of Formula **Ic**



- [00198] and pharmaceutically acceptable salts thereof, wherein:
 [00199] A is NR¹¹R¹²;
 [00200] B is H, -CH₂NH₂, -OMe, -OCH₂CH₂OMe, F, Cl or Me;
 [00201] R¹ is H, F, Cl, Br, Me, cyclopropyl or CN;
 [00202] R^{1a}, R², R³ and R⁴ are independently H, F, Cl, Br, Me or CN;
 [00203] R⁵ and R⁷ are independently H, F, Me or CN;
 [00204] R⁶ is H, F, Me, Br, CN, cyclopropyl, phenyl, MeO- or MeOCH₂CH₂O-;
 [00205] R¹¹ is H or (1-6C)alkyl;
 [00206] R¹² is hetCyc³;
 [00207] hetCyc³ is a 4-7 membered heterocycle having a ring nitrogen atom and optionally substituted with one or more R⁹ groups;
 [00208] each R⁹ is independently selected from (1-6C)alkyl; and
 [00209] p is 0, 1 or 2.
 [00210] In certain embodiments of Formula **Ic**, each of R¹, R², R³, R⁵ and R⁷ is hydrogen.
 [00211] In certain embodiments of Formula **Ic**, B is hydrogen.
 [00212] The compounds of Formula **I** include compounds of Formula **Id**



- [00213] and pharmaceutically acceptable salts thereof, wherein:
- [00214] A is $\text{NR}^{11}\text{R}^{12}$;
- [00215] B is H, $-\text{CH}_2\text{NH}_2$, $-\text{OMe}$, $-\text{OCH}_2\text{CH}_2\text{OMe}$, F, Cl or Me;
- [00216] R^1 is H, F, Cl, Br, Me, cyclopropyl or CN;
- [00217] R^{1a} , R^2 , R^3 and R^4 are independently H, F, Cl, Br, Me or CN;
- [00218] R^5 and R^7 are independently H, F, Me or CN;
- [00219] R^6 is H, F, Me, Br, CN, cyclopropyl, phenyl, MeO- or $\text{MeOCH}_2\text{CH}_2\text{O}-$;
- [00220] R^{11} is H or (1-6C)alkyl;
- [00221] R^{12} is (1-6C alkyl) $\text{NR}^{15}\text{R}^{16}$, $\text{C(O)}(1-6\text{C alkyl})\text{NR}^{15}\text{R}^{16}$, (1-6C alkyl) $\text{NHC(O)}\text{O}(1-6\text{C alkyl})$, or (4-7C)cycloalkyl optionally substituted with OH, NH_2 , $\text{NH}(1-6\text{C alkyl})$ or $\text{N}(1-6\text{C alkyl})_2$; and
- [00222] each R^{15} , R^{17} , R^{16} and R^{18} is independently H or (1-6C)alkyl.
- [00223] In certain embodiments of Formula **Ic**, each of R^1 , R^2 , R^3 , R^5 and R^7 is hydrogen.
- [00224] In certain embodiments of Formula **Ic**, B is hydrogen.
- [00225] The ability of test compounds to act as PIM-1, PIM-2 and/or PIM-3 inhibitors may be demonstrated by the assay described in Examples A, B, and C, respectively.
- [00226] Compounds of Formula **I** have been found to be inhibitors of PIM-1 and/or PIM-2 and/or PIM-3, and are useful for treating diseases and disorders which can be treated with a Pim-1 and/or Pim-2 and/or Pim-3 kinase inhibitor, including diseases mediated by Pim-1 and/or Pim-2 and/or Pim-3 kinases. 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 and solid tumors (e.g., breast cancer, colon cancer, gliomas).
- [00227] Examples of hematological cancers 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), promyelocytic 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. Additional

examples of hematological cancers include myeloproliferative disorders (MPD) such as polycythemia vera (PV), essential thrombocytopenia (ET) and idiopathic primary myelofibrosis (IMF/IPF/PMF). Certain cancers which can be treated with compounds of Formula I are cancers which are derived from T cells or B cells.

[00228] A further embodiment of this invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

[00229] Accordingly, a further embodiment of this invention provides a method of treating cancer in a mammal in need thereof, comprising administering to said mammal a compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment, the cancer is a hematological cancer. In one embodiment, the cancer derives from T cells. In one embodiment, the cancer derives from B cells.

[00230] A further embodiment of this invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer. In one embodiment, the cancer is a hematological cancer. In one embodiment, the cancer derives from T cells. In one embodiment, the cancer derives from B cells.

[00231] Expression of PIM kinases in immune cells is induced by cytokines present during immune responses. Immune cells are critically dependent on cytokines for differentiation and development of effector functions during normal and pathogenic immune responses. Thus, compounds of the invention may be useful for treating diseases and disorders characterized by aberrant cytokine production and responses and/or aberrant immune cell activation.

[00232] Accordingly, another embodiment of the invention provides a method of treating diseases and disorders characterized by aberrant cytokine production and responses and/or aberrant immune cell activation in a mammal in need thereof, comprising administering to the mammal a compound of Formula I or a pharmaceutically acceptable salt thereof. Examples of such diseases and disorders include autoimmune and inflammatory diseases.

[00233] Another embodiment provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the treatment of diseases and disorders characterized by aberrant cytokine production and responses and/or aberrant immune cell activation in a mammal. Examples of such diseases and disorders include autoimmune and inflammatory diseases.

[00234] Particular examples of diseases and disorders which can be treated using a compound of Formula I include transplant rejection and autoimmune diseases and disorders. Examples of autoimmune diseases and disorders include multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease (IBD), Crohn's disease, irritable bowel syndrome, pancreatitis, ulcerative colitis, diverticulosis, Grave's disease, arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis and ankylosing spondylitis), myasthenia gravis, vasculitis, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, scleroderma, asthma, allergy, systemic sclerosis, vitiligo, grave vs. host disease (GVHD), Sjogren's syndrome, glomerulonephritis, IgA nephropathy, and diabetes mellitus (type I).

[00235] As described in further detail in Example E, compounds of Formula I were found to be effective in inhibiting the proliferation of T cells, as well as inhibiting cytokine production by T cells stimulated through T cell receptors and by cytokines in vitro. The effect of these compounds on IL-4 production and IL-22 production supports the utility of compounds of Formula I in treating diseases where these cytokines have been shown to play a role. Particular examples of such diseases include asthma, MS and inflammatory bowel disease (IBD), lupus, psoriasis and rheumatoid arthritis.

[00236] As an extension of the in vitro data, a compound of Formula I was found to be effective at inhibiting the generation of T cells responses to antigen in vivo as assessed by proliferation and cytokine production ex vivo (Example F). Since T cell activation or proliferation and cytokine production are often key components of autoimmune diseases, the data provided in Example F supports the utility of compounds of Formula I in treating diseases associated with T cell proliferation and cytokine production, including autoimmune diseases such as those described herein.

[00237] B cells are also critically dependent on cytokines for production of particular types of immunoglobulins, called antibody (Ab) isotypes, in a process referred to as isotype switching. Over time, isotype switching can be observed in mice which have been immunized with proteins to produce antibodies, which can then be quantified (Shi et al, 1999 Immunity 10:197-206). As demonstrated in Example G, a compound of Formula I was found to be effective at inhibiting the production of cytokine-stimulated Ab isotypes in response to protein immunization. This suggests that compounds of Formula I affect B cells and supports their use in treating autoimmune and inflammatory diseases, including diseases

thought to be associated in part by pathogenic B cell and Ab responses. Examples of such diseases include lupus, multiple sclerosis and rheumatoid arthritis.

[00238] As demonstrated in Example H, a compound of Formula I was found to be effective in a T cell-mediated murine model of experimental autoimmune encephalomyelitis (EAE). Furthermore, as shown in Example I, a compound of Formula I was found to be effective in a second EAE model in which the disease is caused by generating an immune response to a central nervous system (CNS) protein. EAE mimics many of the pathological features of multiple sclerosis (MS), and these models are widely used to model human disease and its treatment.

[00239] T cells also play in role in the inflammatory bowel disease (IBD), which is an autoimmune disease. As demonstrated in Example J, a compound of Formula I was shown to be effective in a T cell-mediated model of this disease.

[00240] Lupus is an autoimmune disease characterized by aberrant T and B cell responses. In particular, lupus patients can exhibit elevated cytokine levels and increased amounts of anti-nuclear antibodies (Abs). In lupus, Abs can deposit in the kidneys and mediate tissue damage resulting in nephritis. In the MRL/lpr mouse, a murine model of lupus, a compound of Formula I was shown to decrease the production of anti-DNA Abs as well as decrease proteinuria, a measure of kidney damage (Example K).

[00241] Taken together, these examples show that a compound of Formula I is effective at preventing T cell responses both in vitro and in vivo and B cell responses in vivo. Further, this concept is put into practice by showing efficacy of a compound of Formula I in animal models of multiple sclerosis, inflammatory bowel disease and lupus, diseases thought to be associated in part with aberrant immune cell responses. These data support the utility of compounds of Formula I in treating diseases associated with immune cells, such as autoimmune and inflammatory conditions.

[00242] Accordingly, certain compounds according to the present invention may be useful for the treatment of inflammatory disorders mediated by T and B cells function, such as rheumatoid arthritis, lupus, multiple sclerosis, and inflammatory bowel disease.

[00243] Another embodiment of this invention provides a method of treating or preventing inflammatory and autoimmune diseases, comprising administering to a mammal in need thereof an effective amount of a compound of Formula I. Examples of diseases which can be treated include inflammatory or autoimmune diseases. In one embodiment, the

disease is multiple sclerosis. In another embodiment, the disease is lupus. In another embodiment, the disease is inflammatory bowel disease.

[00244] A further embodiment of this invention provides a compound of Formula I for use in treating an inflammatory or autoimmune disease. In one embodiment, the disease is multiple sclerosis. In another embodiment, the disease is lupus. In another embodiment, the disease is inflammatory bowel disease.

[00245] A subset of the triazolopyridine compounds disclosed herein was found to have IC_{50} values for Pim-1 that are at least 10 fold less than the IC_{50} values for Pim-2. As a further example, particular triazolopyridine compounds disclosed herein were found to have IC_{50} values for Pim-1 that are at least 100 fold less than the IC_{50} for Pim-2. Accordingly, also provided are triazolopyridine compounds which are highly potent Pim-1 inhibitors and are highly selective for Pim-1 relative to Pim-2.

[00246] A subset of the triazolopyridine compounds disclosed herein were found to have an IC_{50} values for Pim-1 that are at least 10 fold less than the IC_{50} values for Pim-2 and IC_{50} values for Pim-3 approximately equivalent to that observed for Pim-1. As a further example, particular triazolopyridine compounds disclosed herein were found to have IC_{50} values for Pim-1 that are at least 100 fold less than the IC_{50} values for Pim-2, and IC_{50} values for Pim-3 approximately equivalent to that observed for Pim-1. Accordingly, also provided are triazolopyridine compounds which are highly potent Pim-1/Pim-3 dual inhibitors and are highly selective for Pim-1 and Pim-3 relative to Pim-2.

[00247] As used herein, the term treatment includes prophylaxis as well as treatment of an existing condition.

[00248] Accordingly, another aspect of this invention provides a method of treating diseases or medical conditions in a mammal mediated by a Pim-1 and/or Pim-2 and/or Pim-3 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.

[00249] Compounds of Formula I may also be useful as adjuvants to cancer treatment, that is, they can be used in combination with one or more additional drugs, for example a chemotherapeutic that works by the same or by a different mechanism of action.

[00250] Compounds of the present invention may also be used in combination with one or more additional drugs, for example an anti-inflammatory compound, an

immunosuppressive compound or an immunodepleting agent that works by the same or a different mechanism of action.

[00251] 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 Pim-1 and/or Pim-2 and/or Pim-3 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.

[00252] 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.

[00253] 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.

[00254] 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. 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.

[00255] 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.

[00256] 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 and/or Pim-2 and/or Pim-3 kinase-mediated condition.

[00257] According to a further aspect, the present invention provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of a Pim-1 and/or Pim-2 and/or Pim-3 kinase-mediated condition, as defined hereinabove.

[00258] Particular compounds of the invention include:

[00259] 2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-N-(piperidin-4-yl)quinolin-8-amine di-trifluoroacetate;

[00260] 2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)quinolin amine;

[00261] (*trans*)-4-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-ylamino)cyclohexanol;

[00262] (*S*)-2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-N-(pyrrolidin-3-yl)quinolin-8-amine;

[00263] (*R*)-2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-N-(pyrrolidin-3-yl)quinolin-8-amine;

[00264] *tert*-Butyl 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ylamino)propylcarbamate;

[00265] N1-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-yl)propane-1,3-diamine;

[00266] N1-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-yl)-N1-isopentylpropane-1,3-diamine;

[00267] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(piperidin-4-yloxy)quinoline;

[00268] 3-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propan-1-amine;

[00269] (*R*)-2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-8-(pyrrolidin-3-yloxy)quinoline;

[00270] (*S*)-2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-8-(pyrrolidin-3-yloxy)quinoline;

[00271] (2*S*,4*S*)-Methyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-2-carboxylate;

[00272] 2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-8-(piperidin-4-ylmethoxy)quinoline;

[00273] 2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-8-(2-(piperidin-2-yl)ethoxy)quinoline;

[00274] 2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-8-(piperidin-3-ylmethoxy)quinoline;

[00275] (*trans*)-4-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)cyclohexanamine;

[00276] 3-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine;

- [00277] 3-(2-(7-(aminomethyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-ol;
- [00278] (3-(8-isobutoxyquinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)methanamine;
- [00279] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N,N,2,2-tetramethylpropan-1-amine;
- [00280] (1-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)cyclopropyl)methanol;
- [00281] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(neopentyloxy)quinoline;
- [00282] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-ol;
- [00283] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline;
- [00284] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline;
- [00285] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N-ethyl-2,2-dimethylpropan-1-amine;
- [00286] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N,2,2-trimethylpropan-1-amine;
- [00287] 8-(8-azabicyclo[3.2.1]octan-3-yloxy)-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00288] (2S)-3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylpentan-1-amine;
- [00289] (2R)-3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylpentan-1-amine;
- [00290] (2S)-3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylbutan-1-amine;
- [00291] (2R)-3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylbutan-1-amine;
- [00292] (2S)-3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylhexan-1-amine;
- [00293] (2R)-3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylhexan-1-amine;

- [00294] (2S,4R)-methyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-2-carboxylate;
- [00295] 2-(7-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol;
- [00296] 2-(7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol;
- [00297] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-2,2-dimethylpropan-1-amine;
- [00298] 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxamide;
- [00299] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-difluoropropan-1-amine;
- [00300] (cis)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)cyclohexanamine;
- [00301] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-5-fluoroquinolin-8-yloxy)-2,2-dimethylpropan-1-amine;
- [00302] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(pyridin-3-ylmethoxy)quinoline;
- [00303] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(pyridin-4-ylmethoxy)quinoline;
- [00304] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline;
- [00305] Stereoisomer #1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline;
- [00306] Stereoisomer #2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline;
- [00307] Stereoisomer #3 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline;
- [00308] Stereoisomer #4 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline;
- [00309] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(3-fluoroazepan-4-yloxy)quinoline;
- [00310] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline;
- [00311] (2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid;
- [00312] (2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N,N-dimethylpiperidine-2-carboxamide;
- [00313] (2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N-methoxy-N-methylpiperidine-2-carboxamide;

- [00314] ((2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)piperidin-2-yl)methanol;
2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((2S,4S)-2-(methoxymethyl)piperidin-4-yloxy)quinoline;
- [00315] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-7-bromoquinolin-8-yloxy)-2,2-dimethylpropan-1-amine;
- [00316] 2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((*cis*)-3-fluoropiperidin-4-yloxy)quinoline;
- [00317] *cis*-2-(7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-3-fluoropiperidin-4-yloxy)quinoline;
- [00318] (S)-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(pyrrolidin-2-ylmethoxy)quinoline;
- [00319] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propane-1,2-diol;
- [00320] 3-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine;
- [00321] 3-(2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine;
- [00322] 2,2-Dimethyl-3-(2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propan-1-amine;
- [00323] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline;
- [00324] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-methylpiperidin-4-yl)methoxy)quinoline;
- [00325] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-ethylpiperidin-4-yl)methoxy)quinoline;
- [00326] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-(cyclopropylmethyl)piperidin-4-yl)methoxy)quinoline;
- [00327] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-isopropylpiperidin-4-yl)methoxy)quinoline;
- [00328] 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-1-benzylpiperidin-4-ol;
- [00329] 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)piperidin-4-ol;

- [00330]** 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-methoxypiperidin-4-yl)methoxy)quinoline;
- [00331]** 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(pyridin-4-yloxy)quinoline;
- [00332]** 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)pyridin-2-amine;
- [00333]** 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)pyrimidin-2-amine;
- [00334]** 2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)-quinoline;
- [00335]** 2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline;
- [00336]** 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline;
- [00337]** 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline;
- [00338]** 8-((4-fluoropiperidin-4-yl)methoxy)-2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00339]** 8-((cis)-3-fluoropiperidin-4-yloxy)-2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00340]** 2-(4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-fluoropiperidin-1-yl)acetamide;
- [00341]** 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoro-1-methylpiperidin-4-yl)methoxy)quinoline;
- [00342]** 2-(4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-fluoropiperidin-1-yl)ethanol;
- [00343]** 2-(4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-fluoropiperidin-1-yl)ethanol;
- [00344]** (2S,4S)-methyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-2-carboxylate;
- [00345]** 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline;
- [00346]** (S)-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-(piperidin-3-ylmethoxy)quinoline;
- [00347]** Enantiomer 1 of *cis*-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-5-fluoroazepan-4-yloxy)quinoline;

- [00348] Enantiomer 2 of *trans*-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-5-fluoroazepan-4-yloxy)quinoline;
- [00349] Enantiomer 1 of *cis*-8-5-fluoroazepan-4-yloxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00350] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(3,3-difluoropiperidin-4-yloxy)-6-fluoroquinoline;
- [00351] Enantiomer 1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((*cis*)-3-fluoropiperidin-4-yloxy)quinoline;
- [00352] Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((*cis*)-3-fluoropiperidin-4-yloxy)quinoline;
- [00353] Enantiomer 1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((*trans*)-3-fluoropiperidin-4-yloxy)quinoline;
- [00354] Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((*trans*)-3-fluoropiperidin-4-yloxy)quinoline;
- [00355] 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((*trans*)-5-fluoroazepan-4-yloxy)quinoline;
- [00356] Enantiomer 1 of 8-((*trans*)-5-fluoroazepan-4-yloxy)-2-(6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00357] Enantiomer 2 of 8-((*trans*)-5-fluoroazepan-4-yloxy)-2-(6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00358] 3-(8-((*trans*)-5-fluoroazepan-4-yloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile;
- [00359] 2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((*trans*)-5-fluoroazepan-4-yloxy)quinoline;
- [00360] 2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline;
- [00361] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((1-ethyl-4-fluoropiperidin-4-yl)methoxy)quinoline;
- [00362] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoro-1-(2-fluoroethyl)piperidin-4-yl)methoxy)quinoline;
- [00363] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((4-fluoropiperidin-4-yl)methoxy)quinoline;

- [00364] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((3-fluoroazetidin-3-yl)methoxy)quinoline;
- [00365] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((3-fluoroazetidin-3-yl)methoxy)quinoline;
- [00366] 8-((4-fluoropiperidin-4-yl)methoxy)-2-(6-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00367] 6-fluoro-8-((4-fluoropiperidin-4-yl)methoxy)-2-(6-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00368] 8-((4-fluoropiperidin-4-yl)methoxy)-2-(7-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00369] (R)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-3,3-dimethylbutane-1,2-diol;
- [00370] (R)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3,3-dimethylbutane-1,2-diol;
- [00371] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((4-methoxyazepan-4-yl)methoxy)quinoline;
- [00372] 2-(4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)methyl)-4-methoxyazepan-1-yl)ethanol;
- [00373] 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)azepan-4-ol;
- [00374] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-methoxyazepan-4-yl)methoxy)quinoline;
- [00375] Stereoisomer 1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-5-fluoro-1-methylazepan-4-yloxy)quinoline;
- [00376] Stereoisomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-5-fluoro-1-methylazepan-4-yloxy)quinoline;
- [00377] Stereoisomer 3 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-5-fluoro-1-methylazepan-4-yloxy)quinoline;
- [00378] Stereoisomer 4 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-5-fluoro-1-methylazepan-4-yloxy)quinoline;
- [00379] Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((cis)-5-fluoroazepan-4-yloxy)quinoline;
- [00380] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-(*trans*-5-fluoroazepan-4-yloxy)quinoline;

- [00381] 8-((*cis*-4,5)-5-fluoroazepan-4-yloxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00382] 2,2-dimethyl-3-(2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propan-1-amine;
- [00383] 2-(7-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((**3R,4S**)-3-fluoropiperidin-4-yloxy)quinoline;
- [00384] 8-((4-methoxypiperidin-4-yl)methoxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline;
- [00385] 2-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)morpholine;
- [00386] Enantiomer 1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline;
- [00387] Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline;
- [00388] (1-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)cyclopentyl)methanamine;
- [00389] 2-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)butan-1-ol;
- [00390] 2-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-2-ethylbutan-1-ol;
- [00391] 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3,3-dimethylbutan-1-amine;
- [00392] 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((3-fluoropiperidin-3-yl)methoxy)quinoline;
- [00393] N-(3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropyl)-2-fluoroacetamide;
- [00394] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N-(2,2-difluoroethyl)-2,2-dimethylpropan-1-amine;
- [00395] 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethyl-N-(2,2,2-trifluoroethyl)propan-1-amine; and
- [00396] pharmaceutically acceptable salts thereof. Particular mention is made of hydrochloride salts (including dihydrochloride and trihydrochloride salts) and trifluoroacetate salts (including bis-trifluoroacetate salts) of the aforementioned compounds.

Examples

[00397] 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.

[00398] 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 by syringe. Glassware was oven dried and/or heat dried.

BRIEF DESCRIPTION OF THE FIGURES

[00399] Figure 1 shows the amount of ex vivo proliferation in response to the indicated HEL protein concentrations in cells harvested from mice following in vivo priming with HEL protein and 7 days of treatment with the compound of Example 26 (circles) or vehicle control animals (squares).

[00400] Figure 2 shows the amount of ex vivo IFN γ production in response to the indicated HEL protein concentrations in cells harvested from mice following in vivo priming with HEL protein and 7 days of treatment with the compound of Example 26 (circles) or vehicle control (squares).

[00401] Figure 3 shows the levels of HEL antigen-specific IgG, IgG1, IgG2a, IgG2b, and IgG3 antibodies present in mouse serum relative to vehicle control (defined as 100%) following 2 immunizations with protein antigen and 21 days of in vivo treatment with the compound of Example 26.

[00402] Figure 4 shows the mean clinical score over time in experimental autoimmune encephalomyelitis (EAE) disease-induced in mice by adoptive transfer of encephalogenic cells in the absence of further treatment (open squares), in vehicle-treated animals from day 0 to day 26 (solid diamonds), and in animals treated with the compound of Example 26 administered from day 0 to day 26 (open triangles).

[00403] Figure 5 shows the mean clinical EAE disease score versus days post MOG(33-55) peptide immunization for mice treated from day 7 to day 27 with vehicle (solid diamonds) or the compound of Example 26 (open triangles) and for untreated animals (open squares).

[00404] Figure 6 shows the histological score for inflammation (solid bars), gland loss (hatched bars) and erosion (bricked bars) in the colon of normal mice or mice following 21 days of treatment with vehicle or the compound of Example 26 compared to normal mice as indicated in the murine CD4+CD45RBhi adoptive transfer model of inflammatory bowel disease.

[00405] Figure 7 shows the histological score for mucosal thickening in a murine CD4+CD45RBhi adoptive transfer model of inflammatory bowel disease following 21 days of treatment with vehicle (solid bar) or the compound of Example 26 (hatched bar) compared to normal animals (diamond-speckled bars).

[00406] Figure 8 shows the titer of anti-dsDNA auto-antibodies in serum of mice after 79 days of treatment with vehicle (solid black bars) or with the compound of Example 26 (hatched bars) in the MRL/lpr model of lupus versus the titer in normal mice (speckled bar).

[00407] Figure 9 shows the scored levels of proteinuria present in mice over the time course of the experiment in the MRL/lpr model of lupus after treatment with vehicle (filled diamonds) or the compound of Example 26 (open triangles), relative to normal animals (open squares).

Example A

PIM-1 Enzyme Assay

[00408] The assay for the determination of PIM activity is based on the incorporation of [³³P]PO₄ from [γ -³³P]ATP into PIM2tide substrate and capture of the radiolabeled peptide onto a Whatman P81 (phosphocellulose) filter plate. The amount of radiolabeled product is then measured by liquid scintillation counting. The final buffer conditions were as follows: 20 mM K⁺MOPS, pH 7.4, 10 mM MgCl₂, 0.005% Tween-20, 1 mM DTT. Assay mixtures contained 35 μ M [γ -³³P]ATP (20 μ Ci/mL), 7.5 μ M PIM2tide and 0.25 nM PIM-1 in a total volume of 50 μ L. Incubations were carried out for 60 min at 22 °C and quenched with 75 μ L of 200 mM H₃PO₄, filtered through a Whatman P81 plate and washed (1 x 200 μ L and 5 x 100 μ L) with 200 mM H₃PO₄. Liquid scintillation cocktail (50 μ L) was then added per well, and the plate was counted for 30 s/well using a TopCount NXT.

IC₅₀ Determinations:

[00409] Compounds were prepared at 50x the final concentration in DMSO by conducting 3-fold serial dilutions from a 500- μ M intermediate dilution to give a 10-point dosing curve having a high dose of 10 μ M. One- μ L aliquots of these were then transferred to the assay mixtures above to give a final concentration of DMSO of 2%. A standard or

reference compound was typically included on each assay plate to validate that plate. For each plate, percent of control (POC) values were calculated for each well. IC₅₀'s were estimated from the POC's using a standard 4-parameter logistic model. The IC₅₀ is defined as the concentration of inhibitor at which the POC equals 50 for the fitted curve. Compounds of Formula I were found to have an average IC₅₀ below 10 μM when tested in this assay. Specific IC₅₀ values are provided in Table 2.

Example B

PIM-2 Enzyme Assay

[00410] Assay was performed as described in Example A, using 4 μM [γ -³³P]ATP (20 μCi/mL), 1.0 μM PIM2tide and 1.5 nM GST-tagged recombinant full-length human PIM-2 in place of PIM-1. Compounds of Formula I were found to have an average IC₅₀ below 10 μM when tested in this assay. Specific IC₅₀ values are provided in Table 2.

Example C

PIM-3 Enzyme Assay

[00411] Assay was performed as described in Example A, using 30 μM [γ -³³P]ATP (20 μCi/mL), 3.75 μM PIM2tide and 0.5 nM recombinant rat PIM-3 in place of PIM-1. Compounds of Formula I were found to have an average IC₅₀ below 10 μM when tested in this assay. Specific IC₅₀ values are provided in Table 2.

Example D

Cellular Proliferation Assay

[00412] The assay for determination of the antiproliferative activity of multiple Pim inhibitors in the JAK2-driven cell lines was conducted as follows. Cells were plated out to 96-well plates at an initial density of 10,000 cells/well in 95 μL. Compounds were prepared at 20x the final concentration in DMSO by conducting 3-fold serial dilutions to give a 10-point dosing curve having a high dose of 1000 μM. Aliquots (5 μL) of these dilutions were then transferred to the appropriate wells of the 96-well plates containing cells to yield a final DMSO concentration of 0.5%. The cells were then incubated with compound for 72 hours at 37 °C, 5% CO₂. CelltiterBlue reagent (Promega, Catalog #: G8080) was then added (20 μL/well) and incubated at 37 °C, 5% CO₂ for 1-8 hours depending on the cell line being analyzed. The plate was then quantified employing a fluorescence plate reader (Model: Gemini [Molecular Devices]; Settings: 560 nm (Ex)/590 nm (Em) 570 nm (cut-off) [CellTiter Blue Assay]).

[00413] The values for each well were then converted to a percent of untreated control (POC). These POC values were then plotted as a function of compound concentration. A 4-parameter curve-fit analysis was performed for each compound dilution and an IC₅₀ value was calculated from this curve.

[00414] Table 1 provides IC₅₀ values for certain compound of this invention when tested in this assay cell lines A-E listed below (Note: all are commercially available from ATCC®).

Cell lines

- A: PC3 (Androgen independent prostate cancer)
- B: K562 (Ph+ chronic myelogenous leukemia)
- C: MV4-11 (Acute myelogenous leukemia)
- D: BxPC3 (Pancreatic Cancer)
- E: HepG2 (Hepatocellular Carcinoma)
- F: BaF3 (Mouse pro-B-cell line)
- G: BaF3 TEL-JAK2 (Mouse pro-B-cell transformed with TEL-JAK2 fusion)
- H: BaF2 BCR-Abl (Mouse pro-B-cell transformed with BCR-Abl fusion)

[00415] The symbols in Table 1 are relative indicators of the inherent potencies (antiproliferative effect) of compounds of Examples 1, 16, 17, 18 and 26 against multiple cell lines, tested according to the general experimental procedure outlined in Example D. The definitions of the symbols are as follows:

- ND data not determined
- (-) IC₅₀ is ≥ 10 uM
- (+) IC₅₀ is ≤ 10 uM
- (++) IC₅₀ is ≤ 5 uM
- (+++)
IC₅₀ is ≤ 2 uM

TABLE 1

	Cell Line	A	B	C	D	E	F	G	H
Example #									
1		+	-	ND	ND	ND	+++	+++	+
16		++	+	ND	-	-	+++	+++	++
17		+++	+	ND	+	+	+++	+++	+++
18		+++	++	+++	+	+	+++	+++	+++
26		++	+	+++	ND	ND	+++	+++	+++

[00416] Table 2 provides IC₅₀ values for compounds of the invention when tested in the assays of Examples A, B and/or C.

TABLE 2

Example No.	PIM-1 IC ₅₀ (nM)	PIM-2 IC ₅₀ (nM)	PIM-3 IC ₅₀ (nM)
1	1.6	1107	4.4
2	95	10000	448
3	3	807	25
4	22	6025	105
5	5	2021	20
6	32	10000	155
7	5	1045	35
8	16	5573	93
9	4	570	17
10	3	514	13
11	23	2470	33
12	30	4910	77
13	ND	189	9
14	2	562	11
15	16	4219	102

16	1	169	4
17	0.65	134	3
18	1.5	49	2
19	0.70	17	2
20	2	51	5
21	4	1354	ND
22	5	501	25
23	2	144	6
24	0.8	77	4
25	4	686	20
26	3	137	9
27	3	323	13
28	2	143	4
29	5	585	30
30	3	318	13
31	4	413	19
32	4	399	17
33	5	279	19
34	13	1346	51
35	10	1359	48
36	ND	ND	ND
37	ND	ND	ND
38	ND	ND	ND
39	0.55	26	ND
40	12	1277	46
41	4	182	ND
42	0.75	22	ND
43	139	10000	ND
44	63	7473	ND
45	26.9	1734	ND
46	1	96	ND
47	32	1174	41

48	0.70	147	4
49	0.92	100	2
50	12	290	8
51	3	406	10
52	2	110	4
53	NA	NA	NA
54	178	10000	465
55	70	10000	222
56	9	427	24
57	4	484	NA
58	10	204	NA
59	55	2866	98
60	26	1760	NA
61	132	10000	728
62	34	1721	262
63	0.65	101	NA
64	0.64	323	5
65	0.8	174	NA
66	0.8	52	3
67	0.95	69	3
68	1.3	126	10
69	1.6	95	ND
70	0.75	67	ND
71	16	10000	112
72	5.3	588	ND
73	0.96	79	5
74	151	1994	ND
75	263	8935	ND
76	648	10000	ND
77	17	1389	ND
78	8	1278	ND
79	0.2	55	ND

80	2	1163	ND
81	0.45	142	ND
82	3	1035	ND
83	4	193	ND
84	2	73	ND
85	2	105	ND
86	3	142	10
87	167	ND	248
88	8	502	24
89	ND	ND	ND
90	0.4	131	2
91	0.8	39	0.9
92	1	244	3
93	4.4	506	ND
94	19.4	1000	ND
95	9.8	481.8	ND
96	10.8	1000	ND
97	49	1000	ND
98	0.7	661.3	ND
99	17.4	1000	39.7
100	1.5	351.9	2
101	13	1000	ND
102	4.9	439.6	ND
103	1.4	65.6	ND
104	3.9	191.2	ND
105	8.7	409	ND
106	0.5	25.4	ND
107	9.4	1000	ND
108	7.3	489.2	ND
109	4.7	384.1	ND
110	1.9	163.4	ND
111	8.3	1000	ND

112	3.3	299.9	10.1
113	2.2	166.9	8.8
114	0.7	86	ND
115	1.4	222.4	ND
116	11.8	1000	ND
117	1	91.5	ND
118	3	330	ND
119	1.3	573.8	ND
120 Enantiomer 2	11	958.6	10.9
121 Enantiomer 1	30.5	520.2	16.1
122 Enantiomer 2	17.5	1000	23.5
123	0.9	156	ND
124	31	1000	ND
125	1	429.1	ND
126	14.2	353.7	ND
127	4.8	437.7	6.8
128	19.1	1000	79.4
129	4.9	1000	ND
130	5.8	1000	ND
131	2.3	1000	ND
132	1	76.5	ND
133	1.6	141.6	ND
134	10.1	951.8	ND
135	12.6	506.2	ND
136	5.5	361.9	ND

ND: Not determined

Example ET cell in vitro functional assays

[00417] The in vitro assays to assess the effects of the compounds of Examples 16, 18 and 26 on T cells were conducted as described in assays A, B, C and D below. CD4⁺ T cells were isolated from red blood cell-depleted splenocytes of C57Bl/6J mice (Jackson Laboratories, catalog # 000664) using CD4⁺ T cell isolation kit (Miltenyi, catalog # 130-090-860).

[00418] In assay (A), purified CD4⁺ T cells were plated in 96 well plates at 90000 cells/well in 90 μ L. A dilution series of the compounds of Examples 16, 18 and 26 were prepared at 100x the final concentration in DMSO and then diluted 10-fold into complete media (10x stocks). 10 μ L of 10x compound stocks were added to appropriate wells of 96 well plates containing cells and incubated for 1 hour at 37 °C, 5% CO₂. The cell/compound mixtures were then transferred to a 96 well plate coated with anti-CD3 mAb (1 μ g/mL; BD Pharmingen, catalog # 553057) and soluble anti-CD28 mAb (1 μ g/mL; BD Pharmingen, catalog #553294) was added. Plates were cultured at 37 °C, 5% CO₂ for 40 hours. 20 μ L of the culture were removed for determination of proliferation using the CellTitre-Glo™ luminescent assay (Promega, Catalog #G7571) according to the manufacturer's protocol. The plate was quantified on a Packard TopCount instrument using luminescence protocol and data was analyzed using Prism software.

[00419] In assay (B), purified CD4⁺ cells were treated with compound and stimulated as described for assay (A). After 40 hours, supernatants were assayed for IL-2 using R&D duo set ELISA kits (catalog #DY402). ELISA plates were quantified relative to a standard curve using Molecular Devices Versamax Reader at 450nm and Softmax Pro software.

[00420] In assay (C), 1000000 cells/mL of purified CD4⁺ T cells were mixed with 1 μ g/mL anti-CD28, 10 ng/mL IL-4 (R&D Systems cat # 404-ML-010/CF) and 2 μ g/mL anti-IFN γ (R&D Systems cat # AB-485-NA) and placed into plates coated with 1 μ g/mL anti-CD3. After 5 days, cells were harvested, washed and incubated overnight at 37° 5% CO₂. The following day, 50,000 cells were plated into each well of a 96 well plate. A dilution series of compounds were prepared at 200X the final concentration in DMSO, then 10X stocks were prepared by dilution in cell culture media. 10 μ L of 10X stocks were added to the cells in the 96 well plate and incubated for 2 hours at 37 °C, 5% CO₂. Cell/compound mixtures were then transferred to well coated with 0.1 μ g anti-CD3 and incubated at 37 °C,

5% CO₂. Culture supernatants were removed 18 hours later and tested for IL-4 levels by ELISA (R&D Systems catalog # DY404). ELISA plates were quantified relative to a standard curve using Molecular Devices Versamax Reader at 450nm and Softmax Pro software.

[00421] In assay (D), 1,000,000 cells/mL of purified CD4⁺ T cells were mixed with 1 µg/mL anti-CD28, 50 ng/mL IL-6 (R&D Systems cat # 406-ML-025/CF), 1 ng/mL TGFβ (R&D Systems cat # 303-B2-002), 2 µg/mL anti-IL-4 (R&D Systems cat # AB-404-NA), 2 µg/mL anti-IFNγ (R&D Systems cat # AB-485-NA) and placed into plates coated with 1 µg/mL anti-CD3. After 4 days, cells were harvested, washed and 100,000 cells were plated into 96 well plate. A dilution series of compounds were prepared at 200X the final concentration in DMSO, then 10X stocks were prepared by dilution in cell culture media. 10 µL of 10X stocks were added to the cells in the 96 well plate. After 2 hours, 50 ng IL-23 (R&D Systems catalog # 1887-ML-010/CF) was added to each well and 18 hours later supernatants were removed and tested for IL-22 levels by ELISA (R&D Systems catalog # M2200). ELISA plates were quantified relative to a standard curve using Molecular Devices Versamax Reader at 450nm and Softmax Pro software.

[00422] For each of assays A, B, C and D, the values for each well were converted to a percent of vehicle-treated (DMSO) control (POC). These POC values were plotted as a function of compound concentration and an IC₅₀ calculated using a 4-parameter curve-fit analysis program. Table 3 provides relative indicators of the inherent potencies of the compounds of Examples 16, 18 and 26 in assays A, B, C and D.

TABLE 3

Compound of Example #	Proliferation (Assay A)	IL-2 Production (Assay B)	IL-4 Production (Assay C)	IL-22 Production (Assay D)
16	+++	+++	+++	+++
18	+++	+++	+++	+++
26	++	++	++	++

(-) IC₅₀ is ≥ 10 µM

(+) IC₅₀ is ≤ 10 µM

(++) IC₅₀ is ≤ 5 µM

(+++) IC₅₀ is ≤ 1 µM

[00423] The data shown in Table 3 indicate the compounds of Examples 16, 18 and 26 decrease proliferation and cytokine production by T cells. These data support the utility of compounds of Formula I in diseases associated with T cells or the soluble factors (including IL-2, IL-4, IL-22) secreted by these cells.

Example F

T cell in vivo functional assay

[00424] To determine the effect of compounds of Formula I on T cell responses, the following experiment was conducted. On Day 0, C57BL/6 (Jackson Laboratories #000664, 6-8 weeks of age) were immunized at the base of the tail with 100 µg of hen egg lysozyme (HEL; Sigma #L7773) with complete Freund's adjuvant (CFA; Sigma #F5881). Starting on Day 0 and continuing until Day 7, mice were dosed twice a day by oral administration with vehicle (water) or the compound of Example 26 (200 mg/kg). On Day 7, popliteal lymph nodes were removed, single cell suspensions were prepared and 500,000 cells in 200 µL were activated in 96 well plates with the indicated dose of HEL peptide. Following incubation for 72 hours at 37 °C, 5% CO₂, supernatants were harvested for IFN γ ELISA (R&D Systems catalog #MIF00) and proliferation was assessed using the CellTitre-Glo™ luminescent assay (Promega, Catalog #G7571) with both assays performed according to the manufacturer's protocol. ELISA plates were quantified relative to a standard curve using Molecular Devices Versamax Reader at 450 nM and Softmax Pro software; proliferation was quantitated on a Packard TopCount instrument using luminescence protocol and data was analyzed using excel software.

[00425] Figure 1 shows the ex vivo HEL-specific proliferation following 7 days of in vivo treatment with vehicle (squares) or the compound of Example 26 (circles). Figure 2 shows amount of IFN γ production following 7 days of in vivo treatment with vehicle (squares) or the compound of Example 26 (circles). Both HEL-specific proliferation and IFN γ production are decreased relative to vehicle following dosing with a compound of Formula I.

[00426] The data shown in Figures 1 and 2 demonstrate that immunization in the presence of a compound of Formula I impairs the ability to generate a T cell-mediated immune response, and support the utility of compounds of Formula I in treating diseases associated with the immune system.

Example G

B cell in vivo functional assay

[00427] To determine the effect of a compound of Formula I on B cell responses, the following experiment was conducted. On Day 0, C57BL/6J mice (Jackson Laboratories #000664, 6-8 weeks of age) were immunized at the base of the tail with 20 µg of hen egg lysozyme (HEL; Sigma #L7773) with complete Freund's adjuvant (CFA; Sigma #F5881). Mice were re-immunized on day 7 with 20 µg HEL in alum (Pierce catalog #77161). Starting on Day 0 and continuing through Day 28, mice were dosed once a day by oral administration with vehicle (water) or the compound of Example 26 (200 mg/kg). Serum was collected on days 0, 7, 14, 21, and 28 and analyzed for HEL-specific total IgG, IgG1, IgG2a, IgG2b, and IgG3 antibody production by capture ELISA (antibodies purchased from Invitrogen, catalog #M30007, #M32107, #M32307, #M32507, #M32607). ELISA plates were quantitated using Molecular Devices Versamax reader at 450 nM. The group mean titer of each antibody analyte was converted to percent of vehicle control (= 100%).

[00428] Figure 3 shows the percent of vehicle control of HEL-specific total IgG, IgG1, IgG2a, IgG2b, and IgG3 antibodies on Day 21. Mice treated with the compound of Example 26 (hatched bars) have decreased titers of IgG2a, IgG2b and IgG3.

[00429] These data demonstrate that a compound of Formula I can alter the nature of the B-cell antibody response resulting in a different profile of antibody isotypes being produced. Isotypes of antibodies have differential functions. These data therefore support the utility of compounds of Formula I in treating diseases associated with B cells and characterized by pathogenic antibodies.

Example H

Adoptive Transfer Experimental Autoimmune Encephalomyelitis

[00430] Having observed that compounds of Formula I inhibit T cell activation in vitro and in vivo, the effect of a compound of Formula I on an autoimmune disease induced by T cells was determined using an adoptive transfer EAE model, an animal model of human multiple sclerosis (Brain (2006), 129, 1953-1971). This model relies on the injection of T cells from animals with EAE into disease-free host animals. This injection of cells is known to those skilled in the art as adoptive transfer. By injecting the animals with activated, encephalogenic T cells, this model is focused on the pathogenic stage of EAE autoimmune disease. On Day -14, C57BL/6 mice (Taconic Farms; 10 weeks old) were immunized with a disease-causing protein, MOG(35-55) peptide in complete Freund's adjuvant (Hooke

Laboratories, catalog #EK-0113). On Day -3, spleens were harvested, single cell suspensions were prepared and then 5,000,000 cells/mL were stimulated with 20 µg/mL MOG(33-55) peptide (Open Biosystems), 30 ng/mL IL-12 (R&D Systems catalog #419-ML-010), 10 µg/mL anti-IFN γ antibody (BD Biosciences catalog #554408) at 37 °C, 5% CO₂. On Day 0, 1,500,000 of these cells were injected intravenously into the tail veins of C57BL/6 recipient mice. The recipient mice were divided into treatment groups for vehicle (distilled water; 10 mL/kg) or the compound of Example 26 (200 mg/kg), both administered by oral gavage twice daily for 26 days. The recipient mice were scored daily days 0 through 26 using the following clinical scoring system:

0.0 – no symptoms

1.0 – limp tail

2.0 – limp tail and weakness of hind legs

3.0 – limp tail and complete hind limb paralysis, or partial front and hind limb paralysis, or severe head tilting combined with pushing against cage wall and spinning when picked up by tail

4.0 – limp tail, complete hind limb paralysis and partial front limb paralysis

5.0 – Full body paralysis, or spontaneous rolling or found dead due to paralysis

[00431] Figure 4 shows the group mean +/- SEM (standard error of the mean) of clinical score for the duration of the adoptive transfer experiment for the vehicle-treated animals (solid diamonds) and animals treated with the compound of Example 26 (open triangles), relative to untreated animals (open squares). As shown, treatment with the compound of Example 26 resulted in significant delay in disease onset in this model (where "disease onset" is defined by the first of 2 consecutive days with a clinical score greater than or equal to 1). Median day of onset of the untreated and vehicle groups was day 6 while treatment with the compound of Example 26 extended the median day of onset to 11 days. These results support the utility of compounds of Formula I in the treatment of multiple sclerosis.

Example I

MOG(35-55)-induced Experimental Autoimmune Encephalomyelitis

[00432] To further determine the effect of compounds of Formula I on an autoimmune disease associated with T cells and cytokines, a MOG-induced experimental autoimmune encephalomyelitis (EAE) experiment was performed. MOG-induced EAE is an animal model of human multiple sclerosis (Brain (2006), 129, 1953-1971).

[00433] On Day 0, C57BL/6J mice (Jackson Laboratories #000664, 6-8 weeks of age) were injected subcutaneously with 100 μ L of complete Freund's adjuvant (CFA) prepared as a 1:1 emulsion of (a) incomplete Freund's adjuvant (Difco, catalog #263910) containing 8 mg/mL *m. tuberculosis* H37RA (Difco, catalog #231141) and (b) phosphate buffered saline (PBS) containing 1 mg/mL MOG(35-55) peptide (California Peptide Research Inc). On the day 0 and 2, mice were injected intravenously with 200 ng of pertussis toxin (List Biological Laboratories, catalog #181). On day 7, the mice were randomized into treatment groups which received vehicle (distilled water) or the compound of Example 26 (200 mg/kg) administered by oral gavage twice daily from days 7 through 27.

[00434] The mice were scored daily on days 7 through 37 using the following clinical scoring system:

- 0.0 – no symptoms
- 0.5 – tail weakness
- 1.0 – limp tail
- 1.5 – unsteady gait, mild hind limb ataxia
- 2.0 – partial hind limb paralysis (hind limbs carrying weight)
- 2.5 – partial hind limb paralysis (hind limbs not carrying weight)
- 3.0 – full hind limb paralysis
- 3.5 – full hind limb paralysis and partial front limb paralysis
- 4.0 – full body paralysis

[00435] Figure 5 shows daily clinical scores over time as mean +/- SEM for each treatment group. Vehicle-treated mice (filled diamonds) and untreated mice (open squares) developed severe EAE, with median maximal scores reaching 3.0 for both groups. Mice treated with the compound of Example 26 (open triangles) had reduced paralysis with a median maximal score of 1.5.

[00436] These results further demonstrate that treatment with a compound of Formula I is efficacious in decreasing the severity of symptoms in EAE, and further support the utility of compounds of Formula I for the treatment of diseases associated with pathogenic T cell responses, including multiple sclerosis.

Example JCD4+CD45RBhi Adoptive Transfer Inflammatory Bowel Disease

[00437] An adoptive transfer model of inflammatory bowel disease (IBD) was performed to determine the effect of compounds of Formula I on IBD, which is an autoimmune disease associated with T cells and cytokines.

[00438] On Day 0, CD4⁺ T cells were isolated from the spleens of female Balb/cAnNCrI mice (Charles River Laboratories; 12 weeks old) as described in Example E. The resulting cells were labeled with fluorescent antibodies against CD4 and CD45 markers and were sorted by flow cytometry for CD4⁺CD45RBhi cells based on fluorescence. 400,000 CD4⁺CD45RBhi cells were then injected intraperitoneally into C.B17/Icr-Prkdc^{scid}/IcrIcoCrI mice (Charles River Laboratories strain code 236; 12 weeks old). This injection of cells is known to those skilled in the art as adoptive transfer. On Day 21, mice were randomized into groups for oral gavage treatment with vehicle (1% carboxymethylcellulose sodium (CMC)/0.5% Tween 80 once daily; CMC, Sigma catalog #C9481, Tween 80 Sigma catalog #P1754) or the compound of Example 26 (200 mg/kg; twice daily). Treatments continued through Day 42.

[00439] At the conclusion of the study, mice were sacrificed and the distal half of their colons were placed in 10% neutral buffered formalin (Richard Allen Scientific catalog #53120-1) and paraffin embedded, sectioned into 4 μ m slices and stained with hematoxylin and eosin (H&E) for analysis by a board certified veterinary pathologist.

[00440] For each H&E stained section, submucosal edema was quantitated by measuring the distance from the muscularis mucosa to the internal border of the outer muscle layer in a non-tangential area thought to most representative the severity of this change. Mucosal thickness was also measured in a non-tangential area of the section that best represented the overall mucosal thickness. This parameter is indicative of gland elongation and mucosal hyperplasia. The extent of inflammation (macrophage, lymphocyte and polymorphonuclear leukocyte (PMN) infiltrate) was assigned severity scores according to the following criteria:

Normal = 0

Minimal = 1 (generally focal affecting 1-10% of mucosa or if diffuse then minimal)

Mild = 2 (generally focal affecting 11-25% of mucosa or if diffuse then mild)

Moderate = 3 (26-50% of mucosa affected with areas of gland loss replaced by inflammatory cell infiltrate, milder in remaining areas of mucosa)

Marked = 4 (51-75% of mucosa affected with areas of gland loss replaced by inflammatory cell infiltrate, milder in remaining areas of mucosa)

Severe = 5 (76-100% of mucosa affected with areas of gland loss replaced by inflammatory cell infiltrate, milder in remaining areas of mucosa)

[00441] The parameters reflecting epithelial cell loss/damage were scored individually using a % area involved scoring method:

None = 0

1-10% of the mucosa affected = 1

11-25% of the mucosa affected = 2

26-50% of the mucosa affected = 3

51-75% of the mucosa affected = 4

76-100% of the mucosa affected = 5

[00442] Parameters that were scored using % involvement included: colon glandular epithelial loss (this includes crypt epithelial as well as remaining gland epithelial loss), and colon erosion (this reflects loss of surface epithelium and generally is associated with mucosal hemorrhage (reflective of the bleeding seen clinically and at necropsy)).

[00443] The three scored parameters (inflammation, glandular epithelial loss, and erosion) were ultimately summed to arrive at a sum of histopathology scores, which indicates the overall damage and would have a maximum score of 15.

[00444] Figure 6 shows the group mean +/- SEM colon histopathology scores for inflammation (solid bars), gland loss (hatched bars) and erosion (brick bars) in mice that were untreated (left bars), or treated with vehicle (middle bars) or the compound of Example 26 (right bars) following 21 days of treatment. Treatment with the compound of Example 26 resulted in reduced severity of disease as assessed by these histologic endpoints. Figure 7 shows the group mean +/- SEM for histological assessment of colon mucosal thickness for untreated animals (diamond-speckled bars) and for animals treated with vehicle (solid black bars) or the compound of Example 26 (hatched bars). Treatment with the compound of Example 26 resulted in an 84% decrease in mucosal thickening (a sign of tissue injury), relative to vehicle treated animals.

[00445] These results show that treatment with a compound of Formula I is efficacious in decreasing the severity of colon damage in a model of IBD and support the utility of compounds of Formula I for treatment diseases associated with pathogenic T cell responses, including IBD.

Example KMRL/lpr Lupus Model

[00446] MRL/lpr is considered to be an animal model of systemic lupus erythematosus (SLE), an autoimmune disease (Cohen and Maldonado 2003, Current Protocols in Immunology Chapter 15, Unit 15.20). MRL/lpr mice have a defect in the apoptosis of activated lymphocytes and over time develop a spontaneous and severe lymphoproliferative disorder characterized by enlarged lymphoid organs, auto-antibody production and kidney disease resulting in proteinuria. SLE patients also exhibit auto-antibodies, and some patients develop kidney disease. To determine the effect of compounds of Formula I in this model of SLE, the following experiment was conducted.

[00447] MRL/MpJ-Fas^{lpr} and age-matched MRL/MpJ control mice (Jackson Laboratories, catalog #000485 and #000486, respectively) were treated once daily with vehicle (1% CMC/0.5% Tween 80) or twice daily with the compound of Example 26 (200 mg/kg) for 10 weeks. Body weights, lymphadenopathy and urine protein levels were monitored weekly. Urine protein levels were determined with Bayer Albutix dipsticks (Bayer catalog #2191) and scored according to the following scale:

0 = none detected

0.5 = trace amounts

1 = 30 mg/dL

2 = 100 mg/dL

3 = 300 mg/dL

4 = 2000 mg/dL

[00448] Serum levels of anti-ds-DNA antibody were measured by ELISA (Alpha Diagnostic, catalog #5120) on Day 28 and upon study termination. ELISA plates were quantitated using a Molecular Devices Versamax plate reader at 450nm and titers calculated relative using to a standard curve using a 4-parameter curve fit with Softmax Pro software.

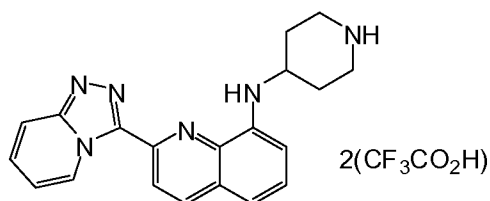
[00449] Treatment with the compound of Example 26 for 28 days resulted in a 74% decrease in serum anti-dsDNA relative to vehicle control animals (data not shown). Figure 8 shows the group mean +/- SEM of anti-dsDNA levels at the termination of the study (79 days of dosing) for untreated animals (speckled bar) and animals treated with vehicle (solid black bar) or the compound of Example 26 (hatched bar). Treatment with compound of Example 26 resulted in a 99% decrease in serum anti-dsDNA antibodies relative to vehicle control animals.

[00450] Figure 9 shows the group mean +/- SEM proteinuria over time for normal animals (open squares) and animals treated with vehicle (filled diamonds) or the compound of Example 26 (open triangles) and demonstrates that treatment with the compound of Example 26 prevents the development of proteinuria relative to vehicle control.

[00451] The results shown in Figures 8 and 9 support the utility of compounds of Formula I in treating some aspects of lupus.

Preparative examples

Example 1



2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-N-(piperidin-4-yl)quinolin-8-amine di-trifluoroacetate

[00452] Step A: Preparation of 8-(tert-butyldimethylsilyloxy)quinoline-2-carbaldehyde: To a solution of 8-hydroxyquinoline-2-carbaldehyde (15.0 g, 86.62 mmol) and imidazole (12.97 g, 190.6 mmol) in anhydrous CH₂Cl₂ (250 mL) at 0 °C was added *tert*-butylchlorodimethylsilane (14.36 g, 95.28 mmol). The mixture was allowed to warm slowly to ambient temperature over 16 hours and then partitioned between CH₂Cl₂ and water. The aqueous phase was extracted with CH₂Cl₂ and the combined organic phases were washed successively with saturated NaHCO₃, water and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel pad filtration eluting with hexanes followed by 19:1 ethyl acetate/hexanes to provide 23.69 g (95%) of desired product as a dark yellow oil.

[00453] Step B: Preparation of (*E/Z*)-8-(*tert*-butyldimethylsilyloxy)-2-((2-(pyridin-2-yl)hydrazono)methyl)quinoline: A solution of 8-(*tert*-butyldimethylsilyloxy)quinoline-2-carbaldehyde (23.40 g, 81.41 mmol) and 2-hydrazinylpyridine (8.88 g, 81.41 mmol) in ethanol (500 mL) was stirred at ambient temperature for 16 hours. The resulting precipitate was filtered, washed with cold ethanol and dried *in vacuo* to provide 30.82 g (82%) of desired product as a beige-colored solid.

[00454] Step C: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(*tert*-butyldimethylsilyloxy)quinoline: To a suspension of (*E/Z*)-8-(*tert*-butyldimethylsilyloxy)-2-((2-(pyridin-2-yl)hydrazono)methyl)quinoline (25.40 g, 67.10 mmol) in anhydrous CH₂Cl₂ (400 mL) was added iodosobenzene diacetate (23.77 g, 73.81 mmol). The mixture was

stirred at ambient temperature for 64 hours after which the solution was partitioned between CH₂Cl₂ and saturated Na₂S₂O₃. The aqueous phase was extracted with CH₂Cl₂ and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated with diethyl ether, filtered and dried *in vacuo* to provide 18.92 g (75%) of desired product as a beige powder.

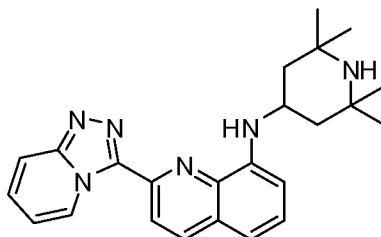
[00455] Step D: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol: To a solution of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(*tert*-butyldimethylsilyloxy) quinoline (18.92 g, 50.25 mmol) in anhydrous THF (400 mL) at 0 °C was added tetrabutylammonium fluoride (75.4 mL, 1.0 M/THF, 75.4 mmol). After stirring for 1 hour at this temperature the mixture was partitioned between saturated NaHCO₃ and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated with CH₂Cl₂, filtered and dried *in vacuo* to provide 11.91 g (90%) of desired product as a beige solid.

[00456] Step E: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yl trifluoromethanesulfonate: To a suspension of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (0.485 g, 1.85 mmol) in a mixture of THF (5 mL) and DMF (2 mL) was added triethylamine (0.57 mL, 4.07 mmol) followed by N-phenyltriflimide (0.727 g, 2.03 mmol). The mixture was stirred at ambient temperature for 16 hours then treated with water (50 mL). The resulting precipitate was filtered, washed successively with water and ether and dried *in vacuo* to provide 0.569 g (78%) of desired product as a light grey solid.

[00457] Step F: Preparation of *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ylamino)piperidine-1-carboxylate: 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yl trifluoromethanesulfonate (0.100 g, 0.25 mmol), *tert*-butyl 4-aminopiperidine-1-carboxylate (0.102 g, 0.51 mmol), Pd₂dba₃ (0.023 g, 0.025 mmol), BINAP (0.032 g, 0.05 mmol) and cesium carbonate (0.124 g, 0.38 mmol) were combined in a capped vial and stirred at 100 °C for 16 hours. The cooled mixture was filtered through GF paper and the filtrate partitioned between saturated NaHCO₃ and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (CH₂Cl₂ followed by 1% MeOH/CH₂Cl₂) to provide 0.107 g (95%) of desired product as an orange foam.

[00458] Step G: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-N-(piperidin-4-yl)quinolin-8-amine di-trifluoroacetate: To a solution of *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ylamino)piperidine-1-carboxylate (0.107 g, 0.241 mmol) in CH₂Cl₂ (4 mL) was added TFA (1 mL). The solution was stirred at ambient temperature for 1 hour then concentrated under reduced pressure. The residue was triturated with ether, filtered and dried *in vacuo* to provide 0.110 g (80%) of desired product as the di-TFA salt. MS ESI (+) *m/z* 345 (M+1) detected.

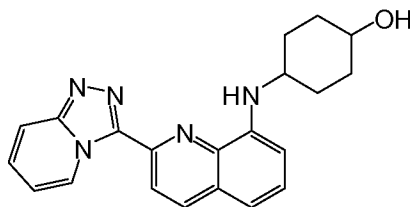
Example 2



2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)quinolin-8-amine

[00459] Prepared as described in Example 1 using *tert*-butyl 4-amino-2,2,6,6-tetramethylpiperidine-1-carboxylate in place of *tert*-butyl 4-aminopiperidine-1-carboxylate in step F. MS ESI (+) *m/z* 401 (M+1) detected.

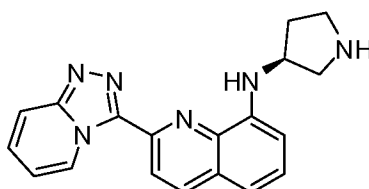
Example 3



(trans)-4-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-ylamino)cyclohexanol

[00460] Prepared as described in Example 1 using *trans*-(1,4)-4-aminocyclohexanol in place of *tert*-butyl 4-aminopiperidine-1-carboxylate in step F. MS APCI (+) *m/z* 360 (M+1) detected.

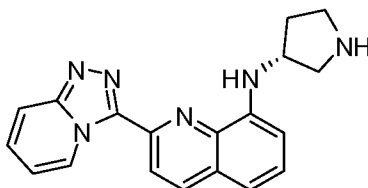
Example 4



(S)-2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-N-(pyrrolidin-3-yl)quinolin-8-amine

[00461] Prepared as described in Example 1 using (S)-tert-butyl 3-aminopyrrolidine-1-carboxylate in place of *tert*-butyl 4-aminopiperidine-1-carboxylate in step F. MS ESI (+) *m/z* 331 (M+1) detected.

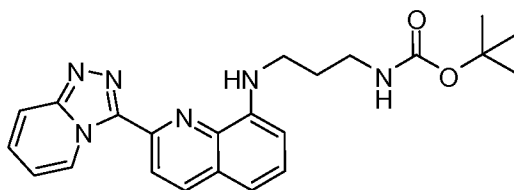
Example 5



(R)-2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-N-(pyrrolidin-3-yl)quinolin-8-amine

[00462] Prepared as described in Example 1 using (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate in place of *tert*-butyl 4-aminopiperidine-1-carboxylate in step F. MS ESI (+) *m/z* 331 (M+1) detected.

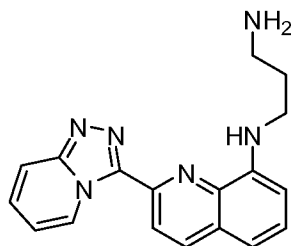
Example 6



tert-Butyl 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ylamino)propylcarbamate

[00463] Prepared as described in Example 1 using *tert*-butyl 3-aminopropylcarbamate in place of *tert*-butyl 4-aminopiperidine-1-carboxylate in step F. MS ESI (+) *m/z* 419 (M+1) detected.

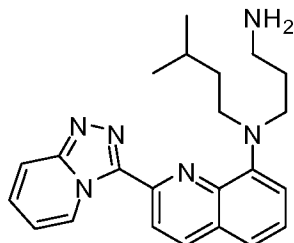
Example 7



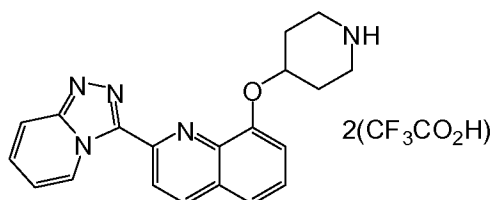
N1-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-yl)propane-1,3-diamine

[00464] Prepared as described in Example 1 using *tert*-butyl 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ylamino)propylcarbamate (Example 6). MS ESI (+) *m/z* 319 (M+1) detected.

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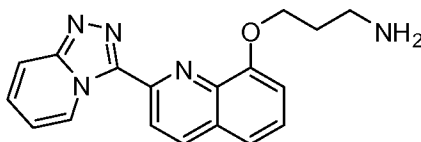
Example 8

N1-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-yl)-N1-isopentylpropane-1,3-diamine
[00465] Prepared as described in Example 1 using *tert*-butyl 3-(isopentylamino)propylcarbamate in place of *tert*-butyl 4-aminopiperidine-1-carboxylate in step F. MS ESI (+) m/z 389 (M+1) detected.

Example 9

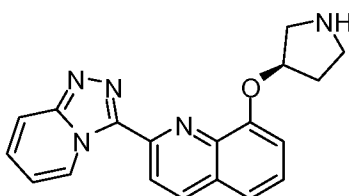
2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(piperidin-4-yloxy)quinoline di-trifluoroacetate
[00466] Step A: Preparation of *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: To a suspension of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (prepared according to Example 1; 112 mg, 0.427 mmol) in anhydrous THF (5 mL) at ambient temperature were added *tert*-butyl 4-hydroxypiperidine-1-carboxylate (95 mg, 0.47 mmol), PPh₃ (168 mg, 0.64 mmol), and DEAD (101 μ L, 0.64 mmol). The resulting yellow solution was stirred for 72 hours and then partitioned between saturated NaHCO₃ and ethyl acetate (20 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organics were dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford a yellow oil. The oil was purified by flash column chromatography using gradient elution (CH₂Cl₂ to 1% MeOH/CH₂Cl₂) to provide the Boc-protected product (90 mg, 47%) as a white foam.
[00467] Step B: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(piperidin-4-yloxy)quinoline di-trifluoroacetate: The product from Step A was dissolved in CH₂Cl₂ (4 mL) and treated with TFA (1 mL). After stirring for 2 hours, the reaction mixture was concentrated to afford a yellow solid. This was triturated with ether, filtered and dried *in vacuo* to afford the desired product as the di-TFA salt, as a white solid. MS ESI (+) m/z 346 (M+1) detected.

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Example 10

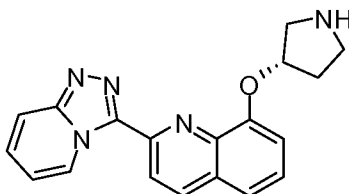
3-(2-((1,2,4)Triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propan-1-amine

[00468] Prepared as described in Example 9 using *tert*-butyl 3-hydroxypropylcarbamate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) m/z 320 (M+1) detected.

Example 11

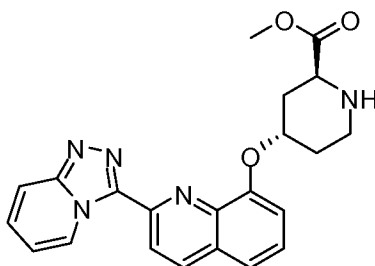
(R)-2-((1,2,4)Triazolo[4,3-a]pyridin-3-yl)-8-(pyrrolidin-3-yloxy)quinoline

[00469] Prepared as described in Example 9 using (*S*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) m/z 332 (M+1) detected.

Example 12

(S)-2-((1,2,4)Triazolo[4,3-a]pyridin-3-yl)-8-(pyrrolidin-3-yloxy)quinoline

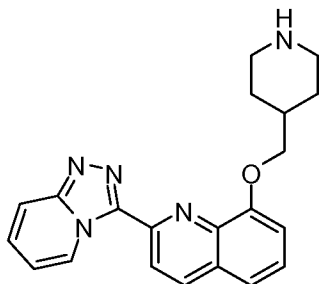
[00470] Prepared as described in Example 9 using (*R*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) m/z 332 (M+1) detected.

Example 13

(2S,4S)-Methyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-2-carboxylate

[00471] Prepared as described in Example 9 using (2S,4R)-1-tert-butyl 2-methyl 4-hydroxypiperidine-1,2-dicarboxylate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) *m/z* 404 (M+1) detected.

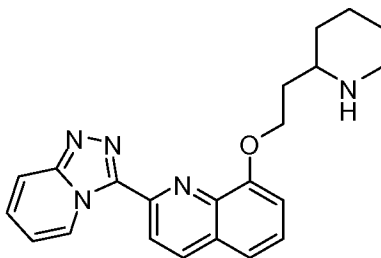
Example 14



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

[00472] Prepared as described in Example 9 using *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) *m/z* 360 (M+1) detected.

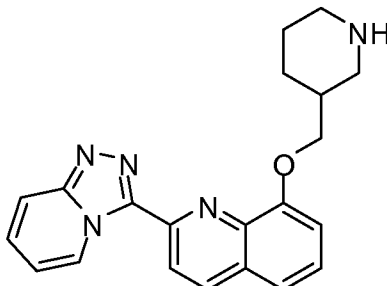
Example 15



2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-8-(2-(piperidin-2-yl)ethoxy)quinoline

[00473] Prepared as described in Example 9 using *tert*-butyl 2-(2-(hydroxyethyl)piperidine-1-carboxylate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) *m/z* 374 (M+1) detected.

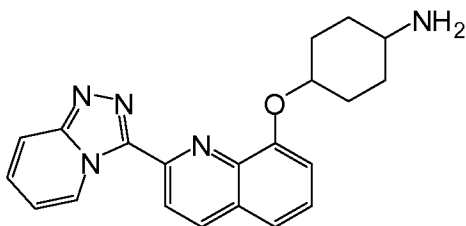
Example 16



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

[00474] Prepared as described in Example 9 using *tert*-butyl 3-(hydroxymethyl)piperidine-1-carboxylate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) m/z 360 (M+1) detected.

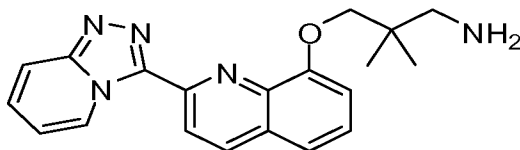
Example 17



(trans)-4-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)cyclohexanamine

[00475] Prepared as described in Example 9 using *cis-tert*-butyl-(1,4)-4-hydroxycyclohexylcarbamate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) m/z 360 (M+1) detected.

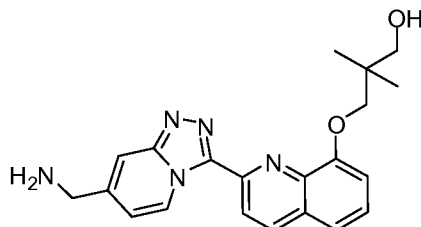
Example 18



3-(2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine

[00476] Prepared as described in Example 9 using *tert*-butyl 3-hydroxy-2,2-dimethylpropylcarbamate as a replacement for *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) m/z 348 (M+1) detected.

Example 19



3-(2-(7-(aminomethyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-ol

[00477] Step A: Preparation of 8-(*tert*-butyldimethylsilyloxy)-2-((*E*)-((*Z*)-(4-iodopyridin-2(1H)-ylidene)hydrazono)methyl)quinoline: To 8-(*tert*-butyldimethylsilyloxy)quinoline-2-carbaldehyde (3.21 g, 11.2 mmol) in DCM (30 mL) was added (*Z*)-1-(4-iodopyridin-2(1H)-ylidene)hydrazine (3.15 g, 13.4 mmol). The reaction was

stirred for 1 hour, affording a yellow precipitate, which was collected by filtration and used without further purification in the next step.

[00478] Step B: Preparation of 8-(tert-butyldimethylsilyloxy)-2-(7-iodo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline: 8-(tert-butyldimethylsilyloxy)-2-((E)-((Z)-(4-iodopyridin-2(1H)-ylidene)hydrazono)methyl)quinoline was weighed into a 1 neck flask and dissolved in THF. Iodobenzene diacetate (IBD) (4.199 g) was added portionwise, and the reaction was stirred for 5 minutes. The reaction was quenched with saturated Na₂S₂O₃ (20 mL). The phases were separated, followed by extraction of the aqueous phase with DCM. The combined organics were dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash column chromatography (eluting with a 2:1 mixture of Hexanes/ethyl acetate), affording the desired product.

[00479] Step C: Preparation of 8-(tert-butyldimethylsilyloxy)-2-(7-vinyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline: To 8-(tert-butyldimethylsilyloxy)-2-(7-iodo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline (2.011 g, 4.003 mmol) in NMP/THF (10 mL/10 mL) was added tributyl(vinyl)stannane (1.523 g, 4.803 mmol), trifuran-2-ylphosphine (0.0929 g, 0.400 mmol), Pd₂dba₃ (0.367 g, 0.4003 mmol) and triethylamine (0.405 g, 4.00 mmol). The reaction was degassed with N₂ and heated to 60 °C for 1 hour. The crude mixture was diluted with ethyl acetate and the organic layer was washed with H₂O. The combined organics fractions were dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash column chromatography (eluting with a 5:1 mixture of Hexanes/ethyl acetate), affording the desired product.

[00480] Step D: Preparation 1-(3-(8-(tert-butyldimethylsilyloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)ethane-1,2-diol: To 8-(tert-butyldimethylsilyloxy)-2-(7-vinyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline (1.321 g, 3.281 mmol) in acetone (10 mL) was added NMO (0.577 g, 4.93 mmol) and OsO₄ (0.5 mL, 3.28 mmol) (0.025% in tBuOH). The reaction was stirred for 4 hours, quenched with saturated Na₂S₂O₃ and concentrated in vacuo. DCM was added to the crude slurry, and the aqueous layer was separated. The organics were dried over Na₂SO₄ and concentrated to provide the crude product.

[00481] Step E: Preparation of 3-(8-(tert-butyldimethylsilyloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-7-carbaldehyde: Sodium periodate (6.060 mL, 3.939 mmol) was added to silica gel (6 g) in DCM (10 mL), affording a slurry. 1-(3-(8-(tert-butyldimethylsilyloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)ethane-1,2-diol (1.433 g, 3.282 mmol) in DCM (10 mL) was added to the slurry and the reaction was stirred for 1

hour. The silica gel was removed by filtration and washed with DCM. The filtrate was concentrated in vacuo to provide the crude product.

[00482] Step F: Preparation of (3-(8-(tert-butyldimethylsilyloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)methanol: NaBH₄ (0.124 g, 3.28 mmol) was added to a solution of 3-(8-(tert-butyldimethylsilyloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-7-carbaldehyde (1.328 g, 3.283 mmol) in MeOH (20 mL) at 0 °C. The cold bath was removed and the reaction allowed to warm to ambient temperature over 1 hour. HCl was added and the solution was concentrated. The residue was triturated with DCM. The resulting solid was filtered and concentrated to provide the crude product.

[00483] Step G: Preparation of 2-((3-(8-(tert-butyldimethylsilyloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)methyl)isoindoline-1,3-dione: DEAD (0.6524 mL, 4.143 mmol) was added to a solution of (3-(8-(tert-butyldimethylsilyloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)methanol (1.123 g, 2.762 mmol), isoindoline-1,3-dione (0.6096 g, 4.143 mmol) and triphenylphosphine (1.087 g, 4.143 mmol) in THF (20 mL) at 0 °C. Following addition, the cold bath was removed and the reaction stirred at ambient temperature for 3 hours. The crude reaction was concentrated and the residue was purified by flash column chromatography (eluting with at 1:4 mixture of ethyl acetate/Hexanes) to afford the desired product mixed with triphenylphosphine oxide.

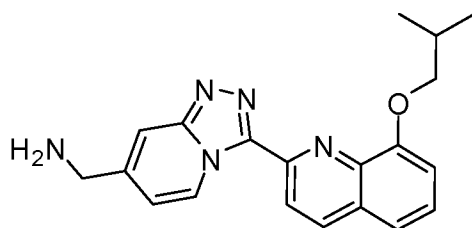
[00484] Step H: Preparation of 2-((3-(8-hydroxyquinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)methyl)isoindoline-1,3-dione: To a solution of 2-((3-(8-(tert-butyldimethylsilyloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)methyl)isoindoline-1,3-dione (1.012 g, 1.889 mmol) and silica gel (3 g) in THF (20mL) was added TBAF (2.267 mL, 2.267 mmol) (1M in THF). The reaction was stirred for 20 minutes, then filtered and washed with DCM/MeOH (10:1). The combined organics were concentrated in vacuo to afford the desired crude product.

[00485] Step I: Preparation of 2-((3-(8-(3-hydroxy-2,2-dimethylpropoxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)methyl)isoindoline-1,3-dione: Cs₂CO₃ (0.513 g, 1.57 mmol) was added to a solution of 2-((3-(8-hydroxyquinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)methyl)isoindoline-1,3-dione (0.221 g, 0.524 mmol) and 3-bromo-2,2-dimethylpropan-1-ol (0.350 g, 2.10 mmol) in DMA (2 mL). The reaction was sealed and heated at 100 °C and stirred for 30 minutes. The reaction was cooled to ambient temperature and diluted with EtOAc/H₂O (2:1). The phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organics were dried over Na₂SO₄ and

concentrated in vacuo. The crude material was purified by flash column chromatography (eluting with a 20:1 mixture of DCM/MeOH), to afford the desired product.

[00486] Step J: Preparation of 3-(2-(7-(aminomethyl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-ol: To a solution of 2-((3-(8-(3-hydroxy-2,2-dimethylpropoxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)methyl)isoindoline-1,3-dione (0.056 g, 0.11 mmol) in EtOH (2 mL) was added hydrazine (0.018 g, 0.55 mmol), and the reaction was stirred for 30 minutes. The reaction was concentrated, and the crude material was purified by flash column chromatography (eluting with a 20:1:0.1 mixture of DCM/MeOH/NH₄OH) to afford the desired product (4 mg). MS ESI (+) *m/z* 378 (M+1) detected.

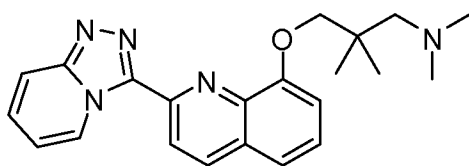
Example 20



(3-(8-isobutoxyquinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-7-yl)methanamine

[00487] Prepared as described in Example 19, using 2-methylpropan-1-ol in place of 3-bromo-2,2-dimethylpropan-1-ol in step I. MS ESI (+) *m/z* 348 (M+1) detected.

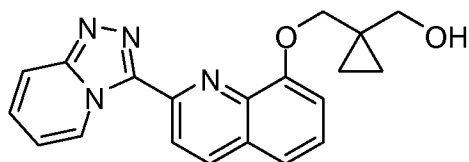
Example 21



3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N,N,2,2-tetramethylpropan-1-amine

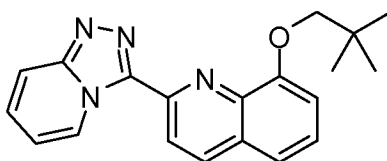
[00488] Prepared as described in Example 9, using 3-(dimethylamino)-2,2-dimethylpropan-1-ol in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) *m/z* 376.2 (M+1) detected.

Example 22

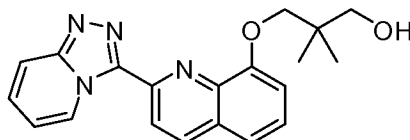


1-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)cyclopropyl)methanol

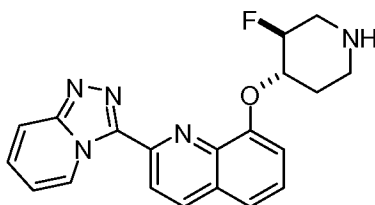
[00489] Prepared as described in Example 9, using 1,1-bis(hydroxymethyl)cyclopropane in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) m/z 347.1 (M+1) detected.

Example 232-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(neopentyloxy)quinoline

[00490] To a solution of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (100 mg, 0.38 mmol), Example 1, Step D, in anhydrous DMA (2 mL) was added cesium carbonate (373 mg, 1.14 mmol) followed by neopentyl iodide (101 μ L, 0.76 mmol). The heterogeneous mixture was stirred at ambient temperature for 2 hours then at 100 °C for 16 hours. The cooled mixture was treated with water (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with water and brine, dried over Na₂SO₄ and concentrated to afford a cream-colored solid. This was triturated with ether and the resulting solid collected by filtration and dried *in vacuo* to provide desired product (62 mg, 49%) as a white powder. MS ESI (+) m/z 333.3 (M+1) detected.

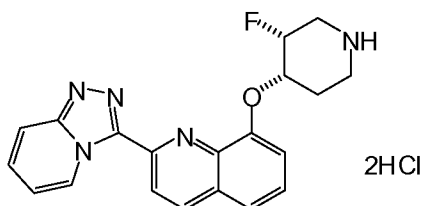
Example 243-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-ol

[00491] Prepared as described in Example 23 using 3-bromo-2,2-dimethylpropan-1-ol in place of neopentyl iodide. MS ESI (+) m/z 349.2 (M+1) detected.

Example 252-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline

[00492] Prepared as described in Example 23 using (cis)-*tert*-butyl-3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate in place of neopentyl iodide. Boc deprotection was achieved as described in Example 9, Step B. MS ESI (+) m/z 364.1 (M+1) detected.

Example 26



2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline dihydrochloride

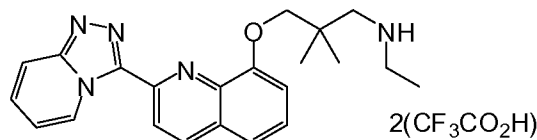
[00493] Prepared as described in Example 23, using (trans)-*tert*-butyl-3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate in place of (cis)-*tert*-butyl-3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate. MS ESI (+) m/z 364.1 (M+1) detected.

[00494] A more detailed description of the synthesis is described in Steps A and B below.

[00495] Step A: Preparation of cis-(3,4)-*tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3-fluoropiperidine-1-carboxylate: 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (5.1 g, 19 mmol), *trans*-(3,4)-*tert*-butyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate (5.8 g, 19 mmol) and cesium carbonate (19 g, 58 mmol) were combined in a round bottom flask and dissolved in 120 mL of DMA and heated at 100 °C overnight, after which the reaction was complete by TLC. The reaction was filtered and the mother liquor concentrated in vacuo. The residue was purified by flash column chromatography, gradient elution 1-10% MeOH/DCM, affording the desired product as a yellow solid containing the starting material 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol as an impurity. MS ESI (+) m/z 464.0 (M+1) detected.

[00496] Step B: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(cis-(3,4)-3-fluoropiperidin-4-yloxy)quinoline dihydrochloride: cis-(3,4)-*tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3-fluoropiperidine-1-carboxylate (9.0 g, 19 mmol) was weighed into a round bottom flask and dissolved in 300 mL of chloroform. HCl (49 mL, 194 mmol) was added dropwise, followed by stirring for 1 hour at ambient temperature, at which time the reaction was complete by LC/TLC. The crude product was collected by filtration, wash with 3 x 100 mL of DCM and then Et₂O, affording the desired product (4.7 g, 13 mmol, 67 % yield) as an off white powder.

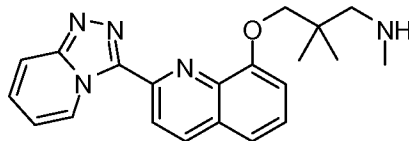
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Example 27

3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N-ethyl-2,2-dimethylpropan-1-amine di-trifluoroacetate

[00497] Step A: Preparation of tert-butyl 3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropyl(ethyl)carbamate: To a solution of *tert*-butyl 3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropylcarbamate (50 mg, 0.11 mmol) in anhydrous DMF (2 mL) was added NaH (7 mg, 60%, 0.17 mmol). After stirring at ambient temperature for 20 min, ethyl iodide (27 μ L, 0.34 mmol) was added and the mixture stirred for a further 5 hrs. The mixture was treated with saturated NH_4Cl (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with water and brine and concentrated to afford a yellow gum. The residue was purified by flash column chromatography using gradient elution (CH_2Cl_2 to 1% MeOH/ CH_2Cl_2 to 2% MeOH/ CH_2Cl_2) to afford desired product (45 mg, 85%) as a colorless gum.

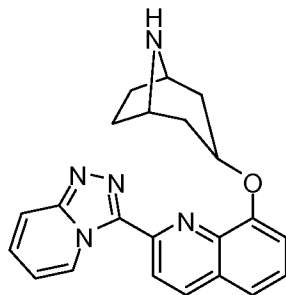
[00498] Step B: Preparation of 3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N-ethyl-2,2-dimethylpropan-1-amine di-trifluoroacetate: To a solution of *tert*-butyl 3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropyl(ethyl)carbamate (45 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) was added TFA (1 mL). The yellow/brown solution was stirred at ambient temperature for 2 hours then concentrated and dried *in vacuo*. The residue was triturated with ether, filtered and dried *in vacuo* to afford desired product (44 mg, 76%) as the di-TFA salt as a white solid. MS APCI (+) m/z 376.2 (M+1) detected.

Example 28

3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N,2,2-trimethylpropan-1-amine

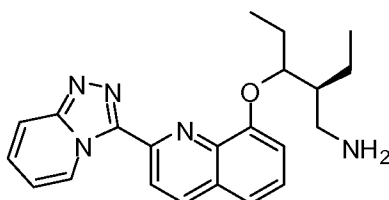
[00499] Prepared as described in Example 27, using methyl iodide in place of ethyl iodide in Step A. MS APCI (+) m/z 362.2 (M+1) detected.

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Example 29

8-(8-azabicyclo[3.2.1]octan-3-yloxy)-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline

[00500] Prepared as described in Example 9, using *tert*-butyl 3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in step A. MS ESI (+) *m/z* 372.2 (M+1) detected.

Example 30

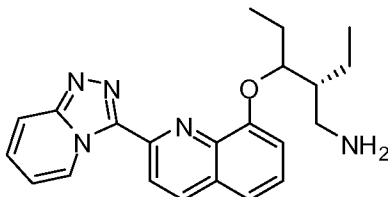
(2S)-3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylpentan-1-amine

[00501] Step A: Preparation of *tert*-butyl (2S)-3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylpentylcarbamate: 2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (101 mg, 0.385 mmol), *tert*-butyl (2S)-2-ethyl-3-hydroxypentylcarbamate (89 mg, 0.385 mmol), PPh₃ (151 mg, 0.577 mmol) and DEAD (90.9 μ L, 0.577 mmol) were combined at ambient temperature in 5 mL anhydrous THF. The reaction mixture was heated at reflux for 6 hours. The crude mixture was cooled to ambient temperature and diluted with water and ethyl acetate. The crude mixture was extracted with ethyl acetate, and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to provide the desired product.

[00502] Step B: Preparation of (2S)-3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylpentan-1-amine: *tert*-Butyl (2S)-3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylpentylcarbamate was dissolved in 5 mL DCM and cooled to 0 °C. TFA (5 mL) was added and the mixture was allowed to warm to ambient temperature over 1 hour. The reaction mixture was evaporated to dryness, and the residue was dissolved in 30 mL DCM and washed with 1N NaOH. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel

chromatography followed by preparative TLC to give the desired product (42.5 mg, 29%).
MS ESI (+) m/z 376.1 (M+1) detected.

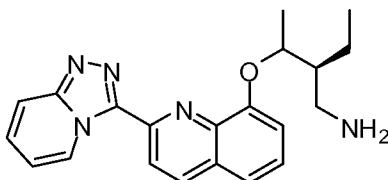
Example 31



(2R)-3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylpentan-1-amine

[00503] Prepared as described in Example 30, using tert-butyl (2R)-2-ethyl-3-hydroxypentylcarbamate in place of tert-butyl (2S)-2-ethyl-3-hydroxypentylcarbamate in step A. MS ESI (+) m/z 376.1 (M+1) detected.

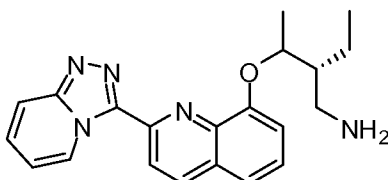
Example 32



(2S)-3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylbutan-1-amine

[00504] Prepared as described in Example 30, using tert-butyl (2S)-2-ethyl-3-hydroxybutylcarbamate in place of tert-butyl (2S)-2-ethyl-3-hydroxypentylcarbamate in step A. MS ESI (+) m/z 362.1 (M+1) detected.

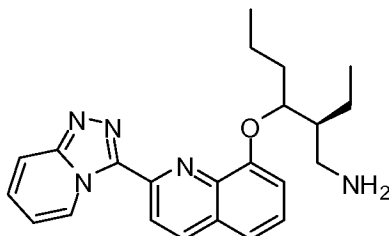
Example 33



(2R)-3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylbutan-1-amine

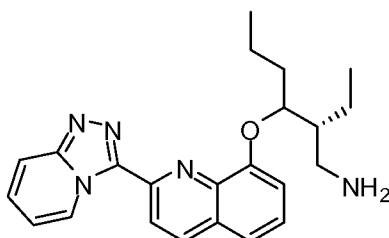
[00505] Prepared as described in Example 30, using tert-butyl (2R)-2-ethyl-3-hydroxybutylcarbamate in place of tert-butyl (2S)-2-ethyl-3-hydroxypentylcarbamate in step A. MS ESI (+) m/z 362.2 (M+1) detected.

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Example 34

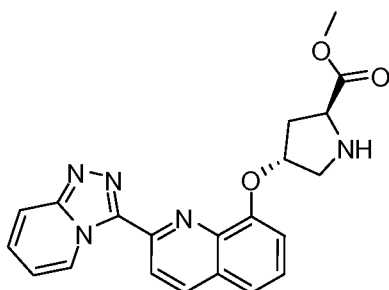
(2S)-3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylhexan-1-amine

[00506] Prepared as described in Example 30, using tert-butyl (2S)-2-ethyl-3-hydroxyhexylcarbamate in place of tert-butyl (2S)-2-ethyl-3-hydroxypentylcarbamate in step A. MS ESI (+) m/z 390.2 (M+1) detected.

Example 35

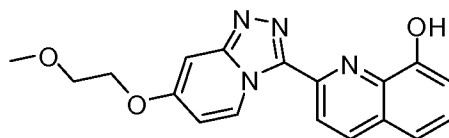
(2R)-3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-ethylhexan-1-amine

[00507] Prepared as described in Example 30 using tert-butyl (2R)-2-ethyl-3-hydroxyhexylcarbamate in place of tert-butyl (2S)-2-ethyl-3-hydroxypentylcarbamate in step A. MS ESI (+) m/z 390.2 (M+1) detected.

Example 36

(2S,4R)-methyl 4-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-2-carboxylate

[00508] Prepared as described in Example 13, using (2S,4S)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate in place (2S,4R)-1-tert-butyl 2-methyl 4-hydroxypiperidine-1,2-dicarboxylate. MS ESI (+) m/z 390.2 (M+1) detected.

Example 372-(7-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol

[00509] Step A: Preparation of 2-chloro-4-(2-methoxyethoxy)pyridine: Potassium 2-methylpropan-2-olate (4.214 g, 35.68 mmol) was slowly added to a solution of 2-chloro-4-nitropyridine (5.142 g, 32.434 mmol) in 2-methoxyethanol (40.0 mL, 506.74 mmol). The reaction was stirred at ambient temperature for 2 hours, then concentrated under reduced pressure. The resulting oil was diluted with water (200 mL) and extracted with Ethyl acetate (2 x 100 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 5.36 g (88 %) of the desired product as a colorless oil.

[00510] Step B: Preparation of 2-hydrazinyl-4-(2-methoxyethoxy)pyridine: Hydrazine (10 mL, 318.6 mmol) was added to a solution of 2-chloro-4-(2-methoxyethoxy)pyridine (1.00 g, 5.330 mmol) in pyridine (25 mL), then heated to reflux. After 18 hours the reaction mixture was partitioned between H₂O and DCM and the aqueous phase was extracted with DCM. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40:1 DCM/MeOH followed by 20:1 DCM/MeOH) to provide 320 mg (33%) of desired product as a white solid.

[00511] Step C: Preparation of 8-(tert-butyldimethylsilyloxy)quinoline-2-carbaldehyde: 8-Hydroxyquinoline-2-carbaldehyde (5.00 g, 28.9 mmol) and imidazole (4.32 g, 63.5 mmol) were dissolved in DCM (50 mL) under N₂. The reaction mixture was cooled to 0 °C, followed by addition of tert-butylchlorodimethylsilane (4.94 g, 31.8 mmol). After stirring for 16 hours at ambient temperature the reaction mixture was partitioned between DCM and H₂O. The organic layer was washed with H₂O and aqueous saturated NaHCO₃, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford an orange oil. The residue was purified by flash column chromatography (10:1 Hexanes/EtOAc) to provide 6.85 g (83%) of desired product as a yellow/orange oil.

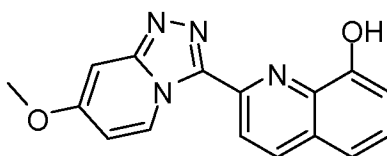
[00512] Step D: Preparation of 8-(tert-butyldimethylsilyloxy)-2-((2-(4-(2-methoxyethoxy)pyridin-2-yl)hydrazono)methyl)quinoline: 2-Hydrazinyl-4-(2-methoxyethoxy) pyridine (0.076 g, 0.415 mmol) and 8-(tert-butyldimethylsilyloxy)

quinoline-2-carbaldehyde (0.119 g, 0.415 mmol) were heated to reflux in EtOH (2 mL) for 16 hours. After cooling to ambient temperature the reaction mixture was filtered and washed with EtOH to provide 105 mg (56%) of desired product as an orange solid.

[00513] Step E: Preparation of 8-(tert-butyldimethylsilyloxy)-2-(7-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline: To a solution of 8-(tert-butyldimethylsilyloxy)-2-((2-(4-(2-methoxyethoxy)pyridin-2-yl)hydrazono)methyl) quinoline (0.101 g, 0.223 mmol) in DCM (1.0 mL) was added iodosobenzene diacetate (0.0719 g, 0.223 mmol). After stirring at ambient temperature for 5 hours the reaction mixture was partitioned between DCM and aqueous saturated Na₂S₂O₃. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40:1 DCM/MeOH) to provide 70 mg (70%) of desired product.

[00514] Step F: Preparation of 2-(7-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol: To a solution of 8-(tert-butyldimethylsilyloxy)-2-(7-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline (0.070 g, 0.155 mmol) in THF (8 mL) was added 1M HCl (1.5 mL, 1.50 mmol). After stirring at ambient temperature for 2 hours, 1 M HCl (5 mL) was added and the reaction mixture stirred for an additional 16 hours. The mixture was neutralized with 1M NaOH and diluted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 40 mg (77%) of desired product. MS APCI (+) *m/z* 337.3 (M+1) detected.

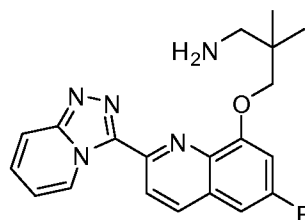
Example 38



2-(7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol

[00515] Prepared as described in Example 37 using the 4-methoxy-2-chloropyridine in place of 2-chloro-4-(2-methoxyethoxy)pyridine. MS APCI (+) *m/z* 293.5 (M+1) detected.

Example 39



3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-2,2-dimethylpropan-1-amine

[00516] Step A: 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 then the combined organics were washed with saturated NaHCO₃, saturated NaCl, dried over Na₂SO₄ and concentrated *in vacuo* to provide the product as a thick dark oil (19 g). MS APCI (+) m/z 178.1 (M+1) detected.

[00517] Step B: 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* to provide the desired product (35 g).

[00518] Step C: 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 and all the filtrates were concentrated *in vacuo*. The crude mixture was chromatographed on SiO₂ eluting with a gradient of 1-5% Et₂O/hexanes to provide the desired product (0.515 g).

[00519] Step D: Preparation of 6-fluoro-2-((2-(pyridin-2-yl)hydrazono)methyl)-8-(triisopropylsilyloxy)quinoline: 6-Fluoro-8-(triisopropylsilyloxy)quinoline-2-carbaldehyde (15.0 g, 43.2 mmol) and 2-hydrazinylpyridine (4.71 g, 43.2 mmol) were combined in 100 mL of anhydrous EtOH, and stirred at ambient temperature over night. Following over night stirring, the desired product was collected by filtration (washing with cold EtOH), affording 6-fluoro-2-((2-(pyridin-2-yl)hydrazono)methyl)-8-(triisopropylsilyloxy)quinoline (14.0 g, 31.9 mmol, 74% yield) as a yellow-white powder.

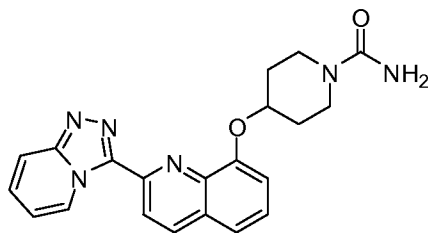
[00520] Step E: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-(triisopropylsilyloxy)quinoline: 6-Fluoro-2-((2-(pyridin-2-yl)hydrazono)methyl)-8-

(triisopropylsilyloxy)quinoline (10 g, 23 mmol) was weighed into a 1000 mL 1 neck round bottom flask, followed by addition of iodo benzene diacetate (8.1 g, 25 mmol) and 400 mL of dichloromethane. The mixture was stirred at ambient temperature for 24 hours, at which time the reaction was complete. The crude mixture was partitioned with $\text{Na}_2\text{S}_2\text{O}_3$, back extracted with DCM, and the combined organics were washed with brine and dried over sodium sulfate, then concentrated in vacuo. The crude product was purified by flash column chromatography (SP1 Biotage Horizon, 1-15% MeOH/DCM gradient elution), affording the desired product (9.4 g, 94% yield) as a white powder.

[00521] Step F: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol: 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-(triisopropylsilyloxy)quinoline (5.00 g, 11.5 mmol) was dissolved in 250 mL of anhydrous THF, followed by cooling to 0 °C, then addition of TBAF (4.49 g, 17.2 mmol). Following 1 hour, the reaction was complete by TLC, and the crude reaction partitioned between water and ethyl acetate. The crude work-up was then filtered through standard filter paper with ethyl acetate wash, affording the desired product 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol (2.8 g, 9.99 mmol, 87% yield) as a white solid.

[00522] Step G: Preparation of: 3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-2,2-dimethylpropan-1-amine: The desired product was prepared as described in Example 25 using 3-(tert-butoxycarbonylamino)-2,2-dimethylpropyl methanesulfonate in place of (cis)-tert-butyl-3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate, and 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol. MS ESI (+) m/z 366 (M+1) detected.

Example 40

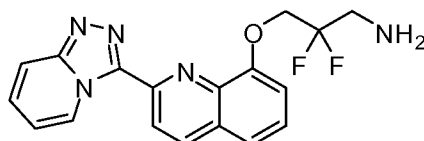


4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxamide

[00523] To a solution of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(piperidin-4-yloxy)quinoline (prepared as described in Example 9, 46 mg, 0.133 mmol) in CH_2Cl_2 (5 mL) were added DIEA (116 μL , 0.67 mmol), DMAP (2 mg, 0.01 mmol), and TMS-isocyanate (104 μL , 0.67 mmol). The reaction mixture was stirred at ambient temperature for 16 hours then partitioned between saturated NaHCO_3 and CH_2Cl_2 . The aqueous layer was extracted

with CH₂Cl₂ and the combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography with gradient elution (CH₂Cl₂ to 1% MeOH/CH₂Cl₂ to 3% MeOH/CH₂Cl₂) to afford desired product (33 mg, 64%) as a colorless glass. MS ESI (+) *m/z* 411.2 (M+Na⁺) detected.

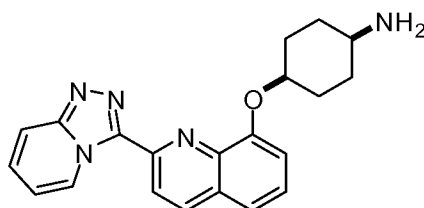
Example 41



3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-difluoropropan-1-amine

[00524] Prepared as described in Example 23 using 3-(tert-butoxycarbonylamino)-2,2-difluoropropyl methanesulfonate in place of neopentyl iodide. Boc deprotection was achieved as described in Example 9, Step B. MS ESI (+) *m/z* 356.2 (M+1) detected.

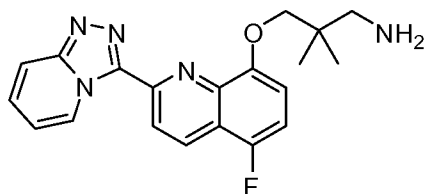
Example 42



(cis)-4-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)cyclohexanamine

[00525] Prepared as described in Example 9, using tert-butyl (trans)-4-hydroxycyclohexylcarbamate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate. MS ESI (+) *m/z* 360.5 (M+1) detected.

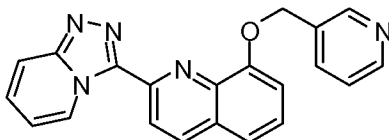
Example 43



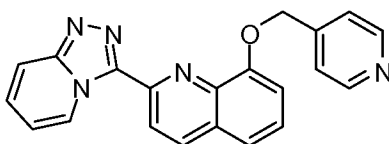
3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-5-fluoroquinolin-8-yloxy)-2,2-dimethylpropan-1-amine

[00526] Prepared as described in Example 39 using 2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-5-fluoroquinolin-8-ol (which was prepared from 2-amino-4-fluorophenol in place of 2-amino-5-fluorophenol in Step A) as a replacement for 2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol. MS ESI (+) *m/z* 366.2 (M+1) detected.

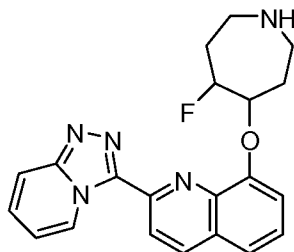
75

Example 442-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(pyridin-3-ylmethoxy)quinoline

[00527] Prepared as described in Example 23 using 3-(iodomethyl)pyridine in place of neopentyl iodide and DMF in place of DMA. MS ESI (+) m/z 354.2 (M+1) detected.

Example 452-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(pyridin-4-ylmethoxy)quinoline

[00528] Prepared as described in Example 23 using 4-(bromomethyl)pyridine in place of neopentyl iodide and DMF in place of DMA. MS ESI (+) m/z 354.1 (M+1) detected.

Example 462-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline

[00529] Step A: Preparation of 1-tert-butyl 4-ethyl 4-fluoro-5-oxoazepane-1,4-dicarboxylate: NaH (2.66 g, 105 mmol) was suspended in THF (300 mL) and cooled to 0 °C, and 1-tert-butyl 4-ethyl 5-oxoazepane-1,4-dicarboxylate (30 g, 105 mmol) was added as THF solution (550 mL) using an addition funnel over 30 minutes. The mixture was stirred for 30 minutes and then diluted with DMF (200 mL). Selectfluor (41.0 g, 116 mmol) was added as a DMF solution (200 mL). The mixture was warmed to ambient temperature and stirred for 2 hours. The mixture was then concentrated to remove THF and diluted with 1N KHSO₄ (300 mL), water (300 mL) and EtOAc (750 mL). The organic layer was washed with brine (2 x 250 mL). The combined aqueous layers were washed with EtOAc (200 mL) and this organic layer was washed with brine (200 mL). The combined organic layers were then dried over

Na₂SO₄, filtered and concentrated. The crude product was passed through a silica gel plug (1 kg, 20 to 40% EtOAc/hexanes) to provide 23.6 g (74%) of the product as a colorless oil.

[00530] Step B: Preparation of *tert*-butyl 4-fluoro-5-oxoazepane-1-carboxylate: To a 500 mL flask containing the product from Step A (23.5 g, 77.5 mmol) was added DMSO (160 mL) followed by H₂O (6.98 mL, 387 mmol) and then LiCl (16.4 g, 387 mmol). The mixture was warmed to 125 °C and stirred for 5 hours. The resulting dark mixture was then cooled to ambient temperature and diluted with EtOAc (500 mL) and washed with a saturated aqueous NaHCO₃:water (1:1, 3 x 250 mL). The combined aqueous phase was washed with EtOAc (100 mL) and the combined organic phases were washed with brine and dried over Na₂SO₄, filtered and concentrated. The crude oil was purified by column chromatography (10 to 30% EtOAc/hexanes) to provide 10.0 g (56%) of the desired product as a light golden oil.

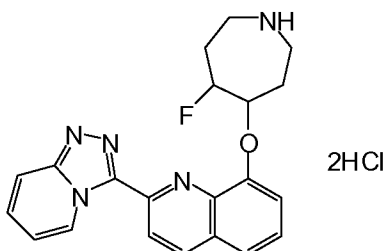
[00531] Step C: Preparation of *tert*-butyl 4-fluoro-5-hydroxyazepane-1-carboxylate: To a 50 mL flask containing the product from Step B (1.0 g, 4.32 mmol) was added MeOH (20 mL), and the resulting solution was cooled to 0 °C. NaBH₄ (0.409 g, 10.8 mmol) was carefully added and the mixture stirred at 0 °C for 3.0 hours. The mixture was concentrated to remove the solvent and the residue was taken up in EtOAc (50 mL) and a saturated aqueous NH₄Cl solution (20 mL) was added followed by water (20 mL). The layers were mixed and separated and the aqueous phase extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried over Na₂SO₄, then filtered and concentrated. The crude product was purified by column chromatography (10% to 60% EtOAc/hexanes gradient) to provide 0.980 g (97%) of the product as a thick colorless oil that solidified to a white solid while standing overnight. The product contained of a mixture of *cis* and *trans* isomers.

[00532] Step D: Preparation of *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate: Prepared as described in Example 9 using the product of Step C in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in Step A and substituting THF:Toluene (1:1) for THF. MS ESI (+) *m/z* 478.1 (M+1) detected.

[00533] Step E: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((5-fluoroazepan-4-yloxy)quinoline: To a solution of *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate (0.157 g, 0.329 mmol) in CHCl₃ (3.2 mL) was added HCl (3.29 mL, 13.2 mmol, 4.0 M in dioxane). The mixture was stirred at ambient temperature for 5 hours and was then filtered directly. The solid was washed with CH₂Cl₂ (5 mL) and Et₂O (5 mL) and carefully dried *in vacuo* to afford the

desired product as an off-white solid. The salt was purified directly by column chromatography (10% MeOH/CH₂Cl₂ with 1% NH₃) to provide the free amine product as an off-white solid. MS ESI (+) *m/z* 378.1 (M+1) detected.

Example 47

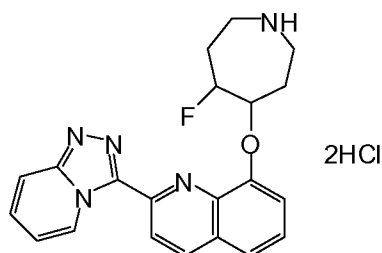


Stereoisomer #1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline dihydrochloride

[00534] Step A: Preparation of Stereoisomer #1 of tert-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate: The racemic material from Example 46 (Step D) was purified by Chiral HPLC OJ-H 85% MeOH/15% EtOH, to provide the first eluting peak as a single stereoisomer (99% ee, 99% de), designated stereoisomer #1.

[00535] Step B: Preparation of Stereoisomer #1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline dihydrochloride: To a 10 mL flask containing the product from Step A (0.138 g, 0.289 mmol) was added CHCl₃ (3.0 mL). To this stirring solution was added HCl (2.89 mL, 11.6 mmol, in dioxane). The mixture was stirred at ambient temperature for 3.0 hours and then filtered directly and washed with CH₂Cl₂ and Et₂O and dried carefully *in vacuo*. This provided 0.120 g (92%) of the desired product as an off-white solid. MS ESI (+) *m/z* 378.1 (M+1) detected.

Example 48



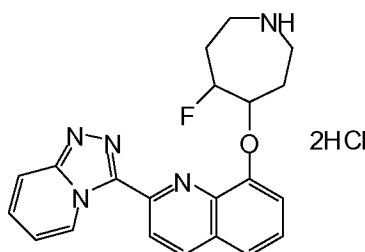
Stereoisomer #2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline dihydrochloride

[00536] Step A: Preparation of Stereoisomer #2 of tert-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate: The racemic material from Example 46 (Step D) was purified by Chiral HPLC OJ-H 85% MeOH/15% EtOH, to provide

the second eluting peak as a single stereoisomer (99% ee, 99% de), designated as stereoisomer #2.

[00537] Step B: Preparation of Stereoisomer #2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline dihydrochloride: Deprotection was performed as described in Example 47, step B. MS ESI (+) m/z 378.1 (M+1) detected. Specific rotation: $[\alpha]_{\text{D}}^{25} = -66^{\circ}$ (c = 0.5, MeOH).

Example 49

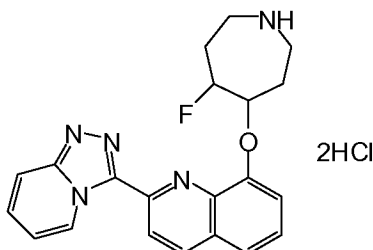


Stereoisomer #3 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline dihydrochloride

[00538] Step A: Preparation of Stereoisomer #3 of *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate: The racemic material from Example 46 (Step D) was purified by Chiral HPLC OJ-H 85% MeOH/15% EtOH, to provide the third eluting peak as a single stereoisomer (99% ee, 99% de), designated as Stereoisomer #3.

[00539] Step B: Preparation of Stereoisomer #3 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline dihydrochloride: Deprotection was performed as described in Example 47, step B. MS ESI (+) m/z 378.1 (M+1) detected. Specific rotation: $[\alpha]_{\text{D}}^{25} = -71^{\circ}$ (c = 0.95, MeOH).

Example 50



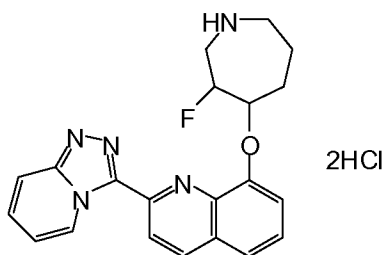
Stereoisomer #4 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline dihydrochloride

[00540] Step A: Preparation of Stereoisomer #4 of *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate: The racemic material from

Example 46 (Step D) was purified by Chiral HPLC OJ-H 85% MeOH/15% EtOH, to provide the fourth eluting peak as a single stereoisomer (99% ee, 60% de), designated as stereoisomer #4.

[00541] Step B: Preparation of Stereoisomer #4 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoroazepan-4-yloxy)quinoline dihydrochloride: Deprotection was performed as described in Example 47, step B. MS ESI (+) m/z 378.1 (M+1) detected.

Example 51



2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(3-fluoroazepan-4-yloxy)quinoline dihydrochloride

[00542] Step A: Preparation of 1-*tert*-butyl 4-ethyl 6-fluoro-5-oxoazepane-1,4-dicarboxylate: A solution of *tert*-butyl 3-fluoro-4-oxopiperidine-1-carboxylate (20.0 g, 92.1 mmol) in 1:1 (CH₂Cl₂:Et₂O, 250 mL) was cooled to -60 °C using an IPA/dry ice bath. In a separate flask was added BF₃-Etherate (12.8 mL, 101 mmol) and Et₂O (40 mL) which was cooled to 0 °C, then ethyl 2-diazoacetate (12.6 mL, 120 mmol) was added. This mixture was added to the oxopiperidine solution and the reaction mixture was slowly warmed to ambient temperature over 2 hours. Water was added (100 mL) and the mixture was stirred at ambient temperature for 30 minutes. The phases were separated and the aqueous phase was extracted with EtOAc (100 mL) and the combined organic phases were washed with 1N KHSO₄, followed by brine and then dried over Na₂SO₄, filtered and concentrated. This provided the product as a thick, yellow oil (26 g).

[00543] Step B: Preparation of *tert*-butyl 3-fluoro-4-oxoazepane-1-carboxylate: The product from Step A was dissolved in DMSO (200 mL) and H₂O (8.29 g, 460 mmol) followed by addition of LiCl (19.5 g, 460 mmol). The solution was warmed to 125 °C and the mixture was stirred overnight. The mixture was cooled to ambient temperature and partitioned between EtOAc (2.5 L) and water:brine (1:1, 2.0 L). The mixture was filtered through activated charcoal over Celite, which was washed with EtOAc, forming visible layers. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (10 to 80% EtOAc/hexanes) providing 4.5 g (21%) of the product as a thick pale orange oil.

[00544] Step C: Preparation of *tert*-butyl 3-fluoro-4-hydroxyazepane-1-carboxylate:

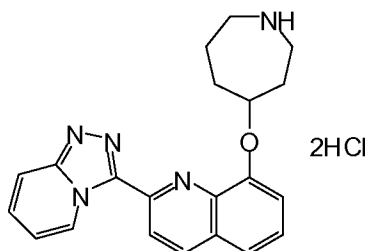
To a solution of the product from Step B (0.300 g, 1.30 mmol) in MeOH (6 mL) at 0 °C was added NaBH₄ (0.123 g, 3.24 mmol) in one portion, and the mixture was warmed to ambient temperature and stirred for 5.0 hours. The mixture was concentrated and the residue was taken up in EtOAc (20 mL) and a saturated aqueous NH₄Cl solution (5 mL) and water (5 mL). The layers were mixed and separated and the aqueous phase extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine and dried over Na₂SO₄, then filtered and concentrated. The crude product was purified by column chromatography (12% to 60% EtOAc/hexanes gradient) to provide 0.130 g (43%) of the major isomer as a colorless oil that solidified overnight to a white solid.

[00545] Step D: Preparation of *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3-fluoroazepane-1-carboxylate:

Prepared as described in Example 9 using *tert*-butyl 3-fluoro-4-hydroxyazepane-1-carboxylate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in Step A, substituting THF:Toluene (1:1) for THF and using DIAD in place of DEAD.

[00546] Step E: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(3-fluoroazepan-4-yloxy)quinoline dihydrochloride:

To a solution of the product from Step D (0.10 g, 0.21 mmol) in CHCl₃ (2.1 mL) was added HCl (2.1 mL, 8.4 mmol, 4.0M in 1,4-Dioxane) and the reaction was stirred at ambient temperature for 5.0 hours. The resulting off-white suspension was directly filtered and the solid was washed with Et₂O and dried *in vacuo*. This provided 0.089 g (88%) of the desired product as an off-white solid. MS ESI (+) *m/z* 378.1 (M+1) detected.

Example 522-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline dihydrochloride**[00547]** Step A: Preparation of *tert*-butyl 4-hydroxyazepane-1-carboxylate:

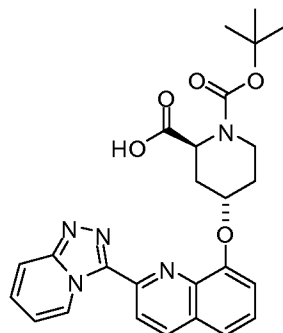
A solution of *tert*-butyl 4-oxoazepane-1-carboxylate (0.60 g, 2.81 mmol), in MeOH (11 mL) was cooled to 0 °C. NaBH₄ (0.266 g, 7.03 mmol) was added and the mixture was slowly warmed to ambient temperature where the reaction stirred overnight. The mixture was concentrated *in*

vacuo and the residue was taken up in EtOAc (20 mL) and saturated aqueous NH₄Cl solution (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine and dried over Na₂SO₄, then filtered and concentrated. The product was isolated as a thick colorless oil that solidified overnight to a white solid.

[00548] Step B: Preparation of *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)quinolin-8-yloxy)azepane-1-carboxylate: Prepared as described in Example 9 using *tert*-butyl 4-hydroxyazepane-1-carboxylate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in Step A and substituting THF:Toluene (1:1) for THF and using DIAD in place of DEAD.

[00549] Step C: Preparation of 2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline dihydrochloride: To a solution of the product from Step B (0.40 g, 0.870 mmol) in CHCl₃ (9 mL) was added hydrogen chloride (7.62 mL, 30.5 mmol, 4.0 M in dioxane) and the reaction was stirred at ambient temperature for 5 hours. The resulting yellow solid was removed by direct filtration and the solid was washed with Et₂O and dried *in vacuo* to provide 0.296 g (72%) of the desired product as a yellow solid. MS ESI (+) *m/z* 360.1 (M+1) detected.

Example 53



(2S,4S)-4-(2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)quinolin-8-yloxy)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid

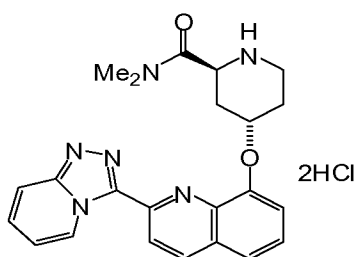
[00550] Step A: Preparation of (2S,4S)-di-*tert*-butyl 4-(2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)quinolin-8-yloxy)piperidine-1,2-dicarboxylate: Prepared as described in Example 9 using di-*tert*-butyl (2S, 4R)-4-hydroxy-1,2-piperidinedicarboxylate (prepared as described in *J. Org. Chem.* **2004**, *69*, 130) in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in Step A and using DIAD in place of DEAD.

[00551] Step B: Preparation of (2S,4S)-4-(2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)quinolin-8-yloxy)-1-piperidine-2-carboxylic acid: A solution of the product from Step A

(1.3 g, 2.38 mmol) in TFA (6.42 mL, 83.4 mmol) was stirred at ambient temperature for 6 hours at which time the reaction was complete by HPLC. TFA was co-evaporated with hexanes and the residue was triturated with Et₂O and filtered. The solid was washed with Et₂O and dried *in vacuo* and taken on directly to the next step.

[00552] Step C: Preparation of (2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid: The product from Step B was then dissolved in THF (7 mL) and H₂O (3 mL) and was treated with NaOH (1.59 mL, 4.77 mmol, 3.0 M aqueous). Boc₂O (0.780 g, 3.57 mmol) was added and the reaction was stirred at ambient temperature overnight. THF was removed *in vacuo* and the residue was dissolved in water (20 mL) and Et₂O (10 mL). The layers were mixed and separated and the aqueous phase extracted with Et₂O (3 x 10 mL). The aqueous phase was adjusted to pH = 2 with 1N KHSO₄. The acidic mixture was extracted with EtOAc (75 mL then 3 x 25mL). The combined organic layers were washed with water and brine, and the combined aqueous phases were washed with EtOAc (50 mL). The combined organic layers were then dried over Na₂SO₄, filtered and concentrated to afford 1.06 g (70% pure, 63% yield) of the product. MS ESI (+) *m/z* 489.9 (M) detected.

Example 54



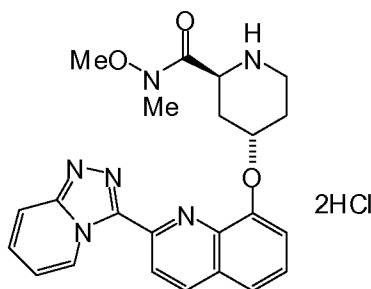
(2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N,N-dimethylpiperidine-2-carboxamide dihydrochloride

[00553] Step A: Preparation of (2S,4S)-tert-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-(dimethylcarbamoyl)piperidine-1-carboxylate: (2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Example 53; 0.100 g, 0.204 mmol), EDCI (0.0548 g, 0.286 mmol) and HOBT (0.0373 g, 0.276 mmol) were mixed in CH₂Cl₂ (2.5 mL) and the mixture was cooled to 0 °C. Triethylamine (0.0712 mL, 0.511 mmol) was added and the mixture stirred for 15 minutes. Dimethylamine (0.153 mL, 0.306 mmol, 2.0M in THF) was added, and the mixture was warmed to ambient temperature and stirred for 5.0 hours. The mixture was diluted with EtOAc (20 mL) and washed with 1N KHSO₄ (2 x 10 mL), followed by saturated aqueous

NaHCO₃, and brine. The organics were dried over MgSO₄, filtered and concentrated, then purified by column chromatography (1 to 5% MeOH/CH₂Cl₂) to afford 0.080 g (75%) of the desired product.

[00554] Step B: Preparation of (2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N,N-dimethylpiperidine-2-carboxamide dihydrochloride: To the product from Step A (0.080 g, 0.155 mmol) was added chloroform (1.6 mL). To the resulting solution was added hydrogen chloride (0.387 mL, 1.55 mmol, 4.0 M in 1,4-dioxane) causing the solution to turn yellow. The mixture was stirred at ambient temperature for 3 hours. Additional hydrogen chloride (0.387 mL, 1.55 mmol, 4.0 M in 1,4-dioxane) was added and the reaction stirred at ambient temperature for another 3 hours. The mixture was diluted with diethyl ether (5 mL) and filtered. The product was washed with Et₂O and dried *in vacuo* to provide 0.068 g (86%) of the desired product as a yellow solid. MS ESI (+) *m/z* 417.1 (M+1) detected.

Example 55

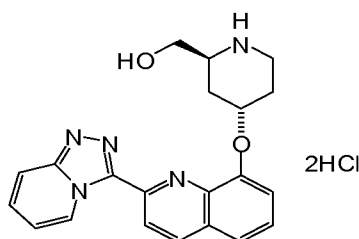


(2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N-methoxy-N-methylpiperidine-2-carboxamide dihydrochloride

[00555] Step A: Preparation of (2S,4S)-tert-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate: (2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Example 53; 0.100 g, 0.204 mmol), EDCI (0.0548 g, 0.286 mmol) and HOBT (0.0359 g, 0.266 mmol) were mixed in CH₂Cl₂ (2.5 mL) and the mixture was cooled to 0 °C. Triethylamine (0.0712 mL, 0.511 mmol) was added and the mixture was stirred for 15 minutes. Dimethyl hydroxylamine HCl (0.0299 g, 0.306 mmol) was added, and the mixture was warmed to ambient temperature and stirred for 4.5 hours. The mixture was diluted with EtOAc (20 mL) and washed with 1N KHSO₄ (2 x 10 mL), followed by a saturated aqueous NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude material was purified by column chromatography (1 to 5% MeOH/CH₂Cl₂) to provide 0.076 g (70%) of the product as a white foam.

[00556] Step B: Preparation of (2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N-methoxy-N-methylpiperidine-2-carboxamide dihydrochloride: To the product from Step A (0.032 g, 0.0601 mmol) was added CHCl_3 (0.600 mL) and HCl (0.451 mL, 1.80 mmol, 4.0M in dioxane). The mixture was stirred at ambient temperature for 9 hours, then diluted with Et_2O (5 mL) and filtered. The solid was washed with Et_2O and dried *in vacuo*. This provided 0.026 g (82%) of the desired product as a pale yellow solid. MS ESI (+) m/z 433.1 (M+1) detected.

Example 56



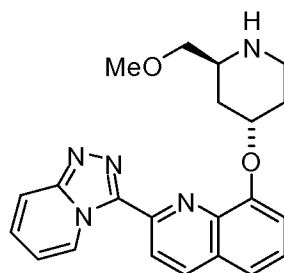
((2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)piperidin-2-yl)methanol dihydrochloride

[00557] Step A: Preparation of (2S,4S)-tert-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-(hydroxymethyl)piperidine-1-carboxylate: (2S,4S)-4-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Example 53; 0.250 g, 0.511 mmol) was dissolved in THF (5.0 mL) and the mixture was cooled to 0 °C. $\text{BH}_3\text{-SMe}_2$ (0.242 mL, 2.55 mmol) was added and the mixture was warmed to ambient temperature and stirred for 27 hours. The reaction was quenched with MeOH (2 mL) and concentrated. The residue was taken up in EtOAc (30 mL), water (5 mL) and a saturated aqueous Na_2CO_3 solution (5 mL). The layers were mixed and separated and the aqueous phase washed once with CH_2Cl_2 (10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 , filtered and concentrated. During concentration a precipitate formed which was slurried in MeOH, isolated by filtration and washed with Et_2O to give 0.119 g (49%) of the desired product as a pale yellow solid.

[00558] Step B: Preparation of ((2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)piperidin-2-yl)methanol dihydrochloride: The product from Step A (0.017 g, 0.036 mmol) was dissolved in CHCl_3 (1.0 mL). HCl (0.27 mL, 1.1 mmol, 4.0M in dioxane) was added. The reaction stirred at ambient temperature for 7 hours. The reaction was diluted with Et_2O (10 mL) and the mixture filtered. The solid was washed with Et_2O and

dried *in vacuo* to afford 0.0098 g (55%) of the desired product as an off-white solid. MS ESI (+) m/z 376.1 (M+1) detected.

Example 57



2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((2S,4S)-2-(methoxymethyl)piperidin-4-yloxy)quinoline

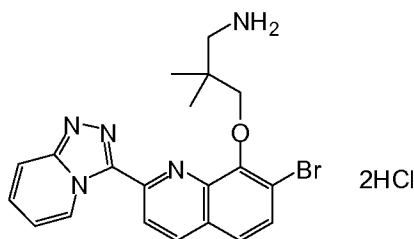
[00559] Step A: Preparation of (2S,4S)-tert-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-(hydroxymethyl)piperidine-1-carboxylate: (2S,4S)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Example 53; 0.250 g, 0.511 mmol) and THF (5.0 mL) was stirred for 10 minutes (until solution was complete) and cooled to 0 °C. $\text{BH}_3\text{-SMe}_2$ (0.242 mL, 2.55 mmol) was added and the mixture was warmed to ambient temperature and for 48 hours. The reaction was carefully quenched with MeOH (1 mL) and concentrated. The residue was taken up in CH_2Cl_2 (20 mL), water (5 mL) and saturated aqueous Na_2CO_3 (5 mL). The layers were mixed and separated and the aqueous phase was washed with CH_2Cl_2 (10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The resulting solid was slurried in 25% $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ and filtered to provide 0.140 g (57%) of the desired product as a yellow solid.

[00560] Step B: Preparation of (2S,4S)-tert-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2-(methoxymethyl)piperidine-1-carboxylate: The product from Step A (0.150 g, 0.315 mmol) was dissolved in dry DMF (2.1 mL) and the solution was cooled to 0 °C. NaH (0.0159 g, 0.631 mmol) was added and the mixture was stirred at 0 °C for 1 hour. The reaction color went from yellow to a dark red/brown. MeI (0.197 mL, 3.15 mmol) was added and the mixture was warmed to ambient temperature and stirred for 2.0 hours during which the reaction color became lighter. The mixture was diluted with saturated aqueous NaHCO_3 (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine and dried over Na_2SO_4 , then filtered and concentrated. The crude product was passed through a silica gel plug to provide the crude

yellow product (0.280 g), which was slurried in 1:1 Et₂O:hexanes and then filtered to provide 0.075 g (48%) of the product as a pale yellow solid.

[00561] Step C: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((2S,4S)-2-(methoxymethyl)piperidin-4-yloxy)quinoline: The product from Step B (0.070 g, 0.14 mmol) was dissolved in CHCl₃ (1.4 mL). Then HCl (1.4 mL, 5.7 mmol, 4.0M in dioxane) was added and the mixture stirred at ambient temperature for 5.0 hours. The mixture was filtered directly and the solid washed with CH₂Cl₂ followed by Et₂O and dried. The crude solid was purified by preparative TLC (1 mm, 8% MeOH/DCM with 1% NH₃). This provided 0.031 g (56%) of the product as a pale orange solid. MS ESI (+) *m/z* 390.2 (M+1) detected.

Example 58



3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-7-bromoquinolin-8-yloxy)-2,2-dimethylpropan-1-amine dihydrochloride

[00562] Step A: Preparation of 7-bromo-2-methylquinolin-8-ol: To a 250 mL flask was added toluene (150 mL) and *t*-BuNH₂ (7.26 mL, 69.1 mmol). The solution was cooled to -25 °C and bromine (1.95 mL, 38.0 mmol) was added. The solution was cooled to -78 °C and 2-methylquinolin-8-ol (5.5 g, 34.6 mmol) was added as a CH₂Cl₂ solution (15 mL). The reaction mixture was gradually warmed to ambient temperature over 6 hours. The mixture was washed with water (50 mL) and treated with 3.0 M aqueous NaOH (250 mL). This provided copious amounts of precipitate, which went into solution after about 600 mL water were added. The layers were mixed and separated. The alkaline extract was carefully acidified with concentrated HCl (~50 mL). The solution was extracted with CH₂Cl₂ (4 x 200 mL), the combined extracts were washed with brine and dried over Na₂SO₄, filtered and concentrated. The original water wash was found to contain a significant amount of product, so 10 mL 1M HCl were added and the acidic solution was extracted with CH₂Cl₂ (2 x 75 mL) and these layers were also washed with brine, dried over Na₂SO₄, filtered and concentrated. The organic phases were combined to provide 5.01 g (60%) of the desired product as a red/brown solid.

[00563] Step B: Preparation of 7-bromo-8-(tert-butyldimethylsilyloxy)-2-methylquinoline: To the product from Step A (3.0 g, 12.6 mmol) was added imidazole (1.89 g, 27.7 mmol) and CH₂Cl₂ (40 mL). The solution was cooled to 0 °C and then *tert*-butylchlorodimethylsilane (2.09 g, 13.9 mmol) was added in one portion. The reaction was gradually warmed to ambient temperature over 1 hour then stirred overnight. The mixture was diluted with a saturated aqueous NH₄Cl solution (25 mL) and CH₂Cl₂ (40 mL). The layers were mixed and separated and the organic layer was washed with brine and dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (2 to 20 % CH₂Cl₂/hexanes) to provide 3.36 g (76%) of the desired product as a white solid.

[00564] Step C: Preparation of 7-bromo-8-(tert-butyldimethylsilyloxy)quinoline-2-carbaldehyde: A slurry of SeO₂ (0.869 g, 7.83 mmol) and 1,4-dioxane (20 mL) was warmed to 80 °C and the product from Step B (2.3 g, 6.53 mmol) was added as a 1,4-dioxane solution (20 mL). The mixture was stirred at 80 °C for 32 hours and then cooled to ambient temperature and filtered through GF/F filter paper. The residual solid was washed with CH₂Cl₂, and the filtrate was concentrated and purified by passing through a silica gel plug, eluting with 50% CH₂Cl₂/hex to provide 2.14 g (89 %) of the product as a yellow/orange solid.

[00565] Step D: Preparation of 7-bromo-8-(tert-butyldimethylsilyloxy)-2-((2-(pyridin-2-yl)hydrazono)methyl)quinoline: To the product from Step C (2.95 g, 8.05 mmol) was added EtOH (30 mL, anhydrous). To this solution was added 2-hydrazinylpyridine (0.967 g, 8.86 mmol). The mixture was stirred at ambient temperature for 24 hours. The resulting precipitate was isolated by vacuum filtration, washed with cold EtOH and then dried *in vacuo* to afford 2.98 g (73%) of the product.

[00566] Step E: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-7-bromo-8-(tert-butyldimethylsilyloxy)quinoline: To the product from Step D (2.95 g, 6.45 mmol) was added CH₂Cl₂ (60 mL). Iodobenzene diacetate (2.28 g, 7.09 mmol) was added and the mixture stirred at ambient temperature overnight. The mixture was concentrated and the product purified directly by column chromatography (1 to 8% MeOH/CH₂Cl₂) to afford 2.87 g (88 %) of the product.

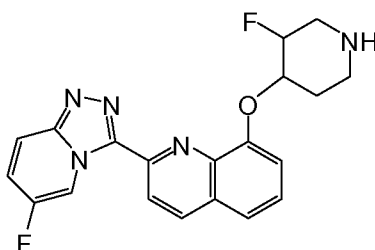
[00567] Step F: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-7-bromoquinolin-8-ol: To the product from Step E (2.8 g, 6.15 mmol) was added THF (60 mL). The solution was cooled to 0 °C then TBAF.3H₂O (2.33 g, 7.38 mmol) was added and the mixture was

stirred for 1 hour. The mixture was then diluted with EtOAc (100 mL) and then washed with saturated aqueous NaHCO₃ (75 mL). The layers were separated and the aqueous phase washed with EtOAc (100 mL). The combined organic phases were washed with brine and dried over Na₂SO₄, filtered and concentrated. The crude mixture was triturated with MeOH and filtered. The solid was washed with Et₂O to provide 0.730 g (35%) of product.

[00568] Step G: Preparation of *tert*-butyl 3-(2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-7-bromoquinolin-8-yloxy)-2,2-dimethylpropylcarbamate: Prepared as described in Example 9 using *tert*-butyl 3-hydroxy-2,2-dimethylpropylcarbamate in place of *tert*-butyl 4-hydroxypiperidine-1-carboxylate in Step A. The crude product was used directly in the next step.

[00569] Step H: Preparation of 3-(2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-7-bromoquinolin-8-yloxy)-2,2-dimethylpropan-1-amine dihydrochloride: To the product from Step G (0.115 g, 0.143 mmol, isolated as a mixture with triphenylphosphine oxide) was added CHCl₃ (1.5 mL). To this solution was added HCl (1.43 mL, 5.72 mmol, 4.0M in dioxane) and the mixture was stirred at ambient temperature for 2.5 hours. The mixture was diluted with CH₂Cl₂ (2 mL) and filtered directly and the resulting solid was washed with CH₂Cl₂ (5 mL) and then with Et₂O. The solid was dried to provide 0.059 g (81%) of the desired product as the di-HCl salt free from triphenylphosphine oxide and as an off-white solid. MS ESI (+) *m/z* 426.1 (M+H) detected.

Example 59



2-(6-fluoro-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-8-((*cis*)-3-fluoropiperidin-4-yloxy)quinoline

[00570] Step A: Preparation of 5-fluoro-2-hydrazinylpyridine: 2-chloro-5-fluoropyridine (5.00 g, 38.01 mmol) was combined with hydrazine monohydrate (15 mL, 303.0 mmol) in a Teflon® lined reactor. The reaction was purged with argon gas and sealed, then heated to 200 °C overnight. Following overnight heating, the reaction mixture was evaporated to solids under reduced pressure, and then dissolved in water containing NaHCO₃. The mixture was transferred to a separatory funnel, and extracted 4 times with EtOAc. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated to residue under

reduced pressure, followed by purification by flash column chromatography eluting with 5% MeOH 0.5% NH₄OH in DCM to give the desired 5-fluoro-2-hydrazinylpyridine (1.50 g, 31% yield). MS APCI (+) m/z 128.0 (M+1) detected.

[00571] Step B: Preparation of 8-(tert-butyldimethylsilyloxy)quinoline-2-carbaldehyde: A solution of 8-hydroxyquinoline-2-carbaldehyde (10.00 g, 57.75 mmol) and imidazole (8.649 g, 127.0 mmol) in DCM (290 mL, 57.75 mmol) was cooled to 0 °C on an ice bath. TBDMS-Cl (9.574 g, 63.52 mmol) was added and the reaction stirred overnight at ambient temperature. Water was added and the reaction transferred to a separatory funnel. The aqueous phase was extracted 3 times with DCM, the organics combined, followed by washes with water and brine. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to residue under reduced pressure. The residue was purified by flash column chromatography, eluting with 25% EtOAc/Hexanes to give the product (12.2 g, 74% yield). MS APCI (+) m/z 288.1 (M+1) detected.

[00572] Step C: Preparation of 8-(tert-butyldimethylsilyloxy)-2-(6-fluoro[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline: 8-(tert-butyldimethylsilyloxy)quinoline-2-carbaldehyde (1.39 g, 4.83 mmol) and 5-fluoro-2-hydrazinylpyridine (1.28 g, 6.04 mmol) were combined in DCM (12.1 mL, 4.83 mmol) at ambient temperature and stirred for 15 minutes. The mixture was cooled to 0 °C followed by addition of iodobenzene diacetate (IBD; 1.87 g, 5.80 mmol). The reaction was warmed to ambient temperature and stirred overnight. Additional IBD (0.8 equivalents, 4.64 mmol) was added and the reaction was allowed to stir at ambient temperature for 48 hours total. The mixture was transferred to a separatory funnel, diluting with water and DCM. The organic phase was washed with saturated aqueous Na₂SO₃, followed by back extraction of the aqueous phase 2 times with DCM. The organics were combined and washed with brine, dried over Na₂SO₄, filtered and concentrated to a residue under reduced pressure, followed by purification by flash column chromatography to give the product (1.08 g, 57% yield). MS APCI (+) m/z 395.3 (M+1) detected.

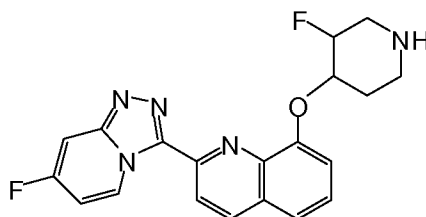
[00573] Step D: Preparation of 2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol: A solution of 8-(tert-butyldimethylsilyloxy)-2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline (560 mg, 1.4195 mmol) in THF (10.13 mL, 1.267 mmol) was cooled to 0 °C in an ice bath. TBAF (1M in THF, 2.122 mL, 2.129 mmol) was added by syringe and the mixture stirred for 1 hour at 0 °C. Water was added, followed by saturated aqueous NaHCO₃ solution. The mixture was transferred to a separatory funnel, diluting with EtOAc and water.

The mixture was extracted with EtOAc, the combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 10-15% MeOH 1% NH₄OH in EtOAc to give the product as a yellow film (35 mg, 9% yield). MS APCI (+) m/z 281.2 (M+1) detected.

[00574] Step E: Preparation of (cis)-tert-butyl 3-fluoro-4-(2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate: A mixture of (trans)-tert-butyl 3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate (24 mg, 0.0807 mmol), 2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (23.8 mg, 0.0850 mmol) and Cs₂CO₃ (55.4 mg, 0.170 mmol) in DMA (425 μl, 0.0850 mmol) was heated to 90 °C for 16 hours. The mixture was transferred to a separatory funnel and diluted with EtOAc and water. The mixture was then extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to a residue under reduced pressure to give the product without further purification (33 mg, 81% yield). MS APCI (+) m/z 481.9 (M+1) detected.

[00575] Step F: Preparation of 2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline: (cis)-tert-butyl 3-fluoro-4-(2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)piperidine-1-carboxylate (33 mg, 0.069 mmol) was dissolved in 2 mL DCM at ambient temperature. TFA (2 mL) was added and the mixture stirred at ambient temperature 1 hour. The reaction was evaporated under reduced pressure, and purified by preparative TLC eluting with 1:10 mixture of (0.5% NH₄OH in MeOH) :DCM to give the product (4.5 mg, 17% yield). MS APCI (+) m/z 382.1 (M+1) detected.

Example 60

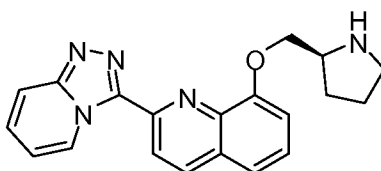


cis-2-(7-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(3-fluoropiperidin-4-yloxy)quinoline

[00576] Prepared as described in Example 59 using 4-fluoro-2-hydrazinylpyridine (as prepared in: *JOC*, **2005**, 70: 2494) in place of 5-fluoro-2-hydrazinylpyridine. MS ESI (+) m/z 382.2 (M+1) detected.

Example 61

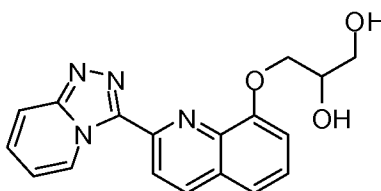
91



(S)-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(pyrrolidin-2-ylmethoxy)quinoline

[00577] Prepared as described in Example 25 using (S)-tert-butyl 2-((methylsulfonyloxy)methyl)pyrrolidine-1-carboxylate in place of (cis)-tert-butyl-3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate. Boc deprotection was achieved as described in Example 9, Step B. MS ESI (+) m/z 346.2 (M+1) detected.

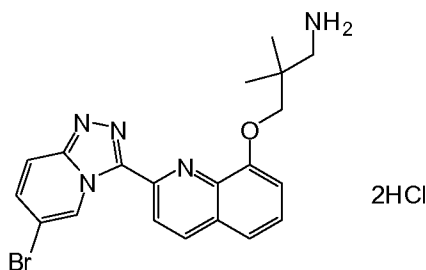
Example 62



3-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propane-1,2-diol

[00578] Prepared as described in Example 9, Step A, using (2,2-dimethyl-1,3-dioxolan-4-yl)methanol in place of tert-butyl 4-hydroxypiperidine-1-carboxylate. Ketal deprotection was achieved as described in Example 9, Step B, using aqueous HCl in place of TFA/DCM. MS ESI (+) m/z 337.1 (M+1) detected.

Example 63



3-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine dihydrochloride

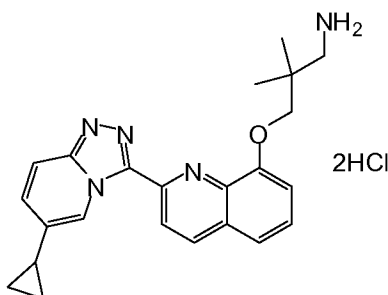
[00579] Step A: Preparation of 2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(tert-butyl dimethylsilyloxy)-quinoline: Prepared as described in Example 1, Steps A – C, using 5-bromo-2-hydrazinylpyridine in place of 2-hydrazinylpyridine.

[00580] Step B: Preparation of 2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol: Prepared as described in Example 1, Step D, using 2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(tert-butyl dimethylsilyloxy)-quinoline in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(tert-butyl dimethylsilyloxy)-

[00581] Step C: Preparation of tert-butyl 3-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropylcarbamate: Prepared as described in Example 9, Step A, using tert-butyl 3-hydroxy-2,2-dimethylpropylcarbamate in place of *tert*-butyl-4-hydroxypiperidine-1-carboxylate and 2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol.

[00582] Step D: Preparation of 3-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine dihydrochloride: To a solution of tert-butyl 3-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropylcarbamate (0.108 g, 0.205 mmol) in 2 mL dichloromethane was added neat TFA (0.395 mL, 5.13 mmol). The reaction mixture was stirred at ambient temperature for 4 hours, after which it was concentrated. The residue was concentrated twice from dichloromethane/hexanes to give solids, which were dried in vacuo. The solids were dissolved in several drops of methanol and minimal dichloromethane, and this solution was added to a vigorously stirring solution of 20 mL ether and 1.5 mL 2M HCl/ether, causing precipitation. The solids were stirred 5 minutes, then isolated by filtration through a medium glass fritted funnel by pushing the solvent through the funnel with nitrogen pressure, rinsed twice with ether, twice with 1:1 dichloromethane:ether, twice with ether, and dried in vacuo to give the title compound (0.042 g, 0.0841 mmol, 41.0 % yield) as a pale yellow powder. MS APCI (+) *m/z* 426/428 (M+1) (Br isotope) detected.

Example 64



3-(2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine dihydrochloride

[00583] Step A: Preparation of 8-(tert-butyl dimethylsilyloxy)-2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline: 2-(6-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(tert-butyl dimethylsilyloxy)quinoline (0.500 g, 1.10 mmol), cyclopropylboronic acid (0.123 g, 1.43 mmol), Pd(OAc)₂ (0.012 g, 0.0549 mmol), P(Cy)₃ (0.031 g, 0.110 mmol), and K₃PO₄ (0.699 g, 3.29 mmol) were combined with 5.5 mL toluene and 0.55 mL H₂O (both degassed

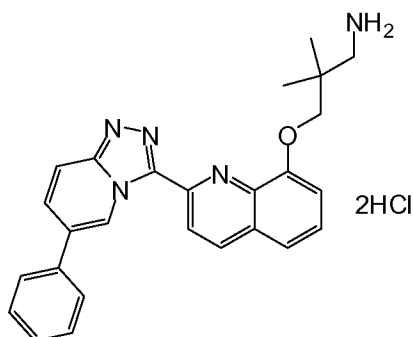
with nitrogen 30 minutes prior to use). The mixture was sonicated and put on a 100 °C reaction block and stirred for 3 hours. The reaction mixture was cooled to ambient temperature, diluted with toluene, vacuum filtered through compressed Celite, rinsed with toluene, and the filtrate was concentrated. The crude material was purified on silica (5% to 60% ethyl acetate in dichloromethane) to give the title compound (0.159 g, 0.382 mmol, 34.8 % yield) as a brown foam.

[00584] Step B: Preparation of 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol: To a 0 °C solution of 8-(tert-butyldimethylsilyloxy)-2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline (0.159 g, 0.382 mmol) in 4 mL THF was added solid TBAF hydrate (0.150 g, 0.573 mmol), causing the reaction mixture to turn cloudy. The reaction mixture was warmed to ambient temperature after 5 minutes and then stirred 17 hours, after which it was diluted with saturated NH₄Cl and water, causing solids to form. The solids were isolated by vacuum filtration through a Buchner funnel, rinsed with water, and air dried in vacuo to give the title compound (0.072 g, 0.238 mmol, 62.4 % yield) as a light pink powder.

[00585] Step C: Preparation of tert-butyl 3-(2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropylcarbamate: Prepared as described in Example 9, Step A, using tert-butyl 3-hydroxy-2,2-dimethylpropylcarbamate in place of *tert*-butyl-4-hydroxypiperidine-1-carboxylate and 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol.

[00586] Step D: Preparation of 3-(2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine dihydrochloride: Prepared as described in Example 63, Step D, using tert-butyl 3-(2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropylcarbamate in place of tert-butyl 3-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropyl-carbamate. MS APCI (+) *m/z* 388 (M+1) detected.

Example 65



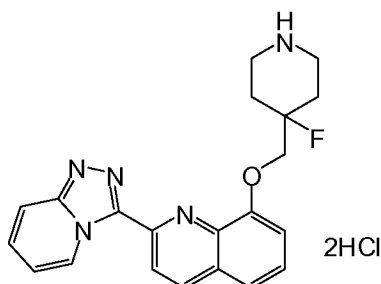
2,2-Dimethyl-3-(2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propan-1-amine dihydrochloride

[00587] Step A: Preparation of 2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol: 2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(tert-butyl dimethylsilyloxy)quinoline (0.500 g, 1.10 mmol), phenylboronic acid (0.167 g, 1.37 mmol), Pd(PPh₃)₄ (0.0634 g, 0.0549 mmol), and 2M aqueous Na₂CO₃ (2.74 mL, 5.49 mmol) (degassed with nitrogen 30 minutes prior to use) were combined with 7 mL dioxane (degassed with nitrogen 30 minutes prior to use), sonicated, and heated to 110 °C in a reaction block for 18 hours, during which the reaction went dry. The reaction mixture was cooled to ambient temperature, diluted with DMF, and the suspension was vacuum filtered through compressed Celite, rinsed with DMF, and the filtrate was concentrated. The crude material was purified on silica gel (1-20% methanol in dichloromethane gradient) to give the title compound (0.138 g, 0.408 mmol, 37.1 % yield) as a brown solid.

[00588] Step B: Preparation of tert-butyl 2,2-dimethyl-3-(2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridine-3-yl)quinolin-8-yloxy)propylcarbamate: Prepared as described in Example 9, Step A, using tert-butyl 3-hydroxy-2,2-dimethylpropylcarbamate in place of *tert*-butyl-4-hydroxypiperidine-1-carboxylate and 2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridine-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridine-3-yl)quinolin-8-ol.

[00589] Step C: Preparation of 2,2-dimethyl-3-(2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridine-3-yl)quinolin-8-yloxy)propan-1-amine dihydrochloride: Prepared as described in Example 63, Step D, using tert-butyl 2,2-dimethyl-3-(2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridine-3-yl)quinolin-8-yloxy)propylcarbamate in place of tert-butyl 3-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-yl)quinolin-8-yloxy)-2,2-dimethylpropyl-carbamate. MS APCI (+) *m/z* 424 (M+1) detected.

Example 66



2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline dihydrochloride

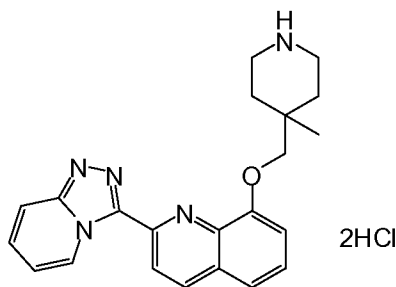
[00590] Step A: Preparation of tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate: To a 0 °C solution of 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (3.0 g, 10.90 mmol) in 55 mL THF was added 1M lithium aluminum hydride in THF (21.79 mL, 21.79 mmol). The reaction mixture was stirred at 0 °C for 3.5 hours, after which it was carefully quenched by the addition of 1:1 Na₂SO₄·10H₂O: Celite, diluted with THF, warmed to ambient temperature, and stirred vigorously for 2 hours. The slurry was vacuum filtered through GF/F paper on a Buchner funnel, rinsed with THF, and the filtrate was concentrated in vacuo to give the title compound (2.69 g) as a clear colorless oil, which was used without further purification.

[00591] Step B: Preparation of tert-butyl 4-fluoro-4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate: To a 0 °C solution of tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (2.60 g, 11.1 mmol) and triethylamine (2.33 mL, 16.7 mmol) in 55 mL dichloromethane was added neat methanesulfonyl chloride (0.949 mL, 12.3 mmol) dropwise by syringe. The reaction mixture was slowly warmed to ambient temperature and stirred at ambient temperature for 17 hours. Saturated NaHCO₃ was added, the mixture was extracted with dichloromethane, and combined extracts were dried (Na₂SO₄), filtered, and concentrated. The crude was purified on silica gel (4:1 hexanes: ethyl acetate to 1:1 hexanes: ethyl acetate) to give the title compound (3.2 g, 92.2 % yield) as a white powder.

[00592] Step C: Preparation of tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yl)oxy)methyl)-4-fluoropiperidine-1-carboxylate: Prepared as described in Example 23 using tert-butyl 4-fluoro-4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate in place of neopentyl iodide. MS APCI (+) *m/z* 478 (M+1) detected.

[00593] Step D: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline dihydrochloride: Prepared as described in Example 63, Step D, using tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yl)oxy)methyl)-4-fluoropiperidine-1-carboxylate in place of tert-butyl 3-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yl)oxy)-2,2-dimethylpropyl-carbamate. MS APCI (+) *m/z* 378 (M+1) detected.

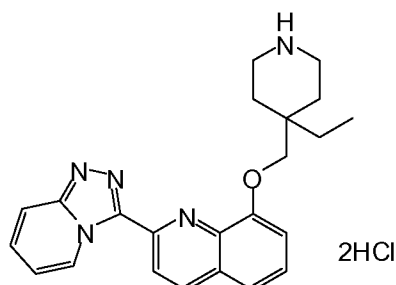
96

Example 67

2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-methylpiperidin-4-yl)methoxy)quinoline dihydrochloride

[00594] Step A: Preparation of tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-methylpiperidine-1-carboxylate: Prepared according to the method of Example 66, Steps A-C, using 1-tert-butyl 4-ethyl 4-methylpiperidine-1,4-dicarboxylate in place of 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate. MS APCI (+) m/z 474 (M+1) detected.

[00595] Step B: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-methylpiperidin-4-yl)methoxy)quinoline dihydrochloride: Prepared according to the method of Example 63, Step D, using tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-methyl-piperidine-1-carboxylate in place of tert-butyl 3-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-yl)quinolin-8-yloxy)-2,2-dimethylpropyl-carbamate. MS APCI (+) m/z 374 (M+1) detected.

Example 68

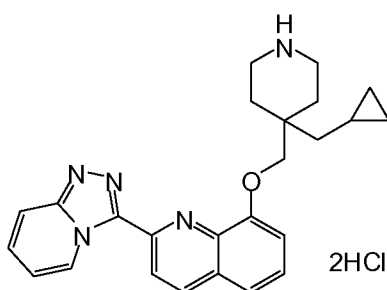
2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-ethylpiperidin-4-yl)methoxy)quinoline dihydrochloride

[00596] Step A: Preparation of 1-tert-butyl 4-ethyl 4-ethylpiperidine-1,4-dicarboxylate: To a 0 °C solution of methyl piperidine-4-carboxylate (2.0 g, 14.0 mmol) in 35 mL THF was added 1M LHMDS in THF (27.9 mL, 27.9 mmol). The reaction mixture was stirred at 0 °C for 90 minutes, then neat iodoethane (3.91 mL, 48.9 mmol) was added slowly by syringe. The reaction mixture was stirred 10 minutes, warmed to ambient temperature,

and stirred 18 hours. Saturated NH_4Cl was added, the mixture was extracted with ethyl acetate, and the combined extracts were dried (Na_2SO_4), filtered, and concentrated. The crude was purified on silica gel eluting with 10:1 hexanes:ethyl acetate to give the title compound (0.843 g, 3.11 mmol, 22.2 % yield) as a clear, colorless oil.

[00597] Step B: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-ethylpiperidin-4-yl)methoxy)quinoline dihydrochloride: Prepared as described for Example 66 using 1-tert-butyl 4-ethyl 4-methylpiperidine-1,4-dicarboxylate in place of 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate. MS APCI (+) m/z 388 (M+1) detected.

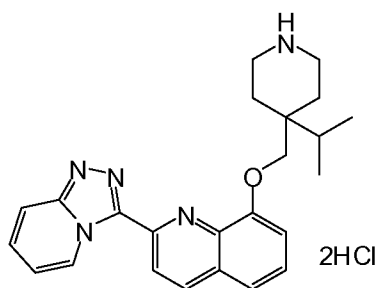
Example 69



2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-(cyclopropylmethyl)piperidin-4-yl)methoxy)quinoline dihydrochloride

[00598] Prepared as described for Example 68 using (bromomethyl)cyclopropane in place of iodoethane. MS APCI (+) m/z 414 (M+1) detected.

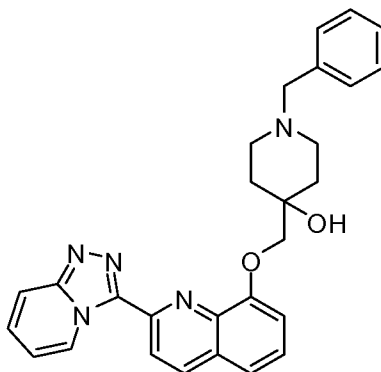
Example 70



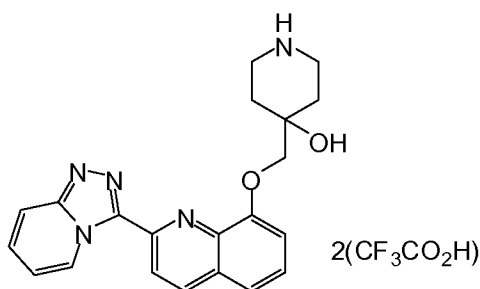
2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-isopropylpiperidin-4-yl)methoxy)quinoline dihydrochloride

[00599] Prepared as described for Example 68 using 2-iodopropane in place of iodoethane. MS APCI (+) m/z 402 (M+1) detected.

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Example 71

4-((2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-1-benzylpiperidin-4-ol
[00600] Prepared as described in Example 23 using 6-benzyl-1-oxa-6-azaspiro[2.5]octane in place of neopentyl iodide. MS APCI (+) m/z 466 (M+1) detected.

Example 72

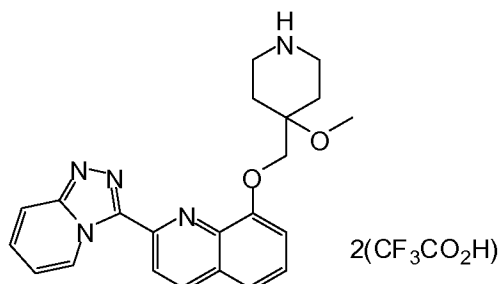
4-((2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)piperidin-4-ol
bis(trifluoroacetate)

[00601] Step A: Preparation of tert-butyl 4-((2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-hydroxypiperidine-1-carboxylate: Prepared as described in Example 23 using tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate in place of neopentyl iodide.

[00602] Step B: Preparation of 4-((2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-piperidin-4-ol bis(trifluoroacetate): To a solution of tert-butyl 4-((2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-hydroxypiperidine-1-carboxylate (0.006 g, 0.013 mmol) in 0.15 mL dichloromethane was added neat TFA (0.029 mL, 0.37 mmol). The reaction mixture was stirred at ambient temperature for 5 hours, after which it was concentrated to dryness. The residue was dissolved in dichloromethane, and the resulting solution was added dropwise to vigorously stirring ether, causing precipitation. The resulting solids were isolated by filtration through a 0.2 micron nylon filter disc, rinsed with

ether, and dried in vacuo to give the title compound (0.005 g, 65.7 % yield) as a pale yellow powder. MS APCI (+) m/z 376 (M+1) detected.

Example 73

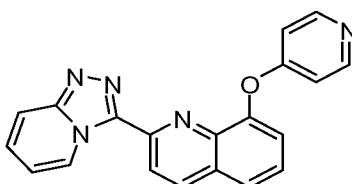


2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-methoxypiperidin-4-yl)methoxy)quinoline bis(trifluoroacetate)

[00603] Step A: Preparation of tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-methoxypiperidine-1-carboxylate: To a 0 °C suspension of tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-hydroxypiperidine-1-carboxylate (0.033 g, 0.069 mmol) in 2 mL DMF was added 60% NaH in mineral oil (0.0117 g, 0.486 mmol). The reaction mixture was warmed to ambient temperature and stirred 2 hours. Neat iodomethane (0.035 mL, 0.56 mmol) was added, and the reaction mixture was stirred for 21 hours. The reaction mixture was concentrated, and the residue was diluted with saturated NH₄Cl and extracted with dichloromethane. The combined extracts were dried (Na₂SO₄), filtered, and concentrated. The crude was purified by preparative TLC (0.5 mm plate, 9:1 dichloromethane: methanol) to give the title compound (0.016 g, 47.1 % yield) as a yellow residue.

[00604] Step B: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-methoxypiperidin-4-yl)methoxy)quinoline bis(trifluoroacetate): Prepared as described for Example 72, Step B, using tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-methyl)-4-methoxypiperidine-1-carboxylate in place of tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-hydroxypiperidine-1-carboxylate. MS APCI (+) m/z 390 (M+1) detected.

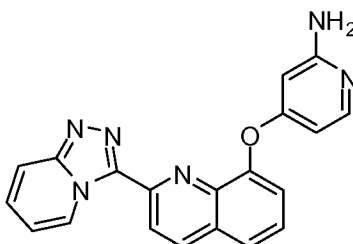
Example 74



2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(pyridin-4-yloxy)quinoline

[00605] Prepared as described in Example 23 using 4-fluoropyridine hydrochloride (which was converted to the free base in situ with diisopropylethylamine) in place of neopentyl iodide. MS APCI (+) m/z 340 (M+1) detected.

Example 75

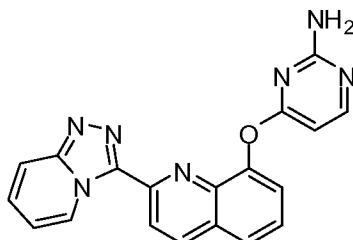


4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)pyridin-2-amine

[00606] Step A: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(2-chloropyridin-4-yloxy)quinoline: Prepared as described in Example 23 using 2-chloro-4-nitropyridine in place of neopentyl iodide. MS APCI (+) m/z 374 (M+1) detected.

[00607] Step B: Preparation of 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)pyridin-2-amine: To a solution of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(2-chloropyridin-4-yloxy)quinoline (0.105 g, 0.281 mmol) in 71 mL THF (degassed with nitrogen 30 minutes prior to use) was added sequentially XPHOS (0.0107 g, 0.0225 mmol), Pd₂dba₃ (0.0103 g, 0.0112 mmol), and 1M LHMDS in THF (0.590 mL, 0.590 mmol) by syringe. The reaction mixture was heated to reflux and stirred for 3 hours. The reaction mixture was cooled to 0 °C and 1M aqueous HCl (1.40 mL, 1.40 mmol) was added, causing milky solids to form. The reaction mixture was stirred 30 minutes, then diluted with water and dichloromethane, and the aqueous layer was washed with dichloromethane. The aqueous layer was basified with 1M NaOH (pH>10), and the milky mixture was extracted with chloroform. The combined extracts were dried (Na₂SO₄), filtered, and concentrated. The crude was purified by preparative TLC (9:1 chloroform:6% NH₄OH in methanol) to give the title compound (0.027 g, 0.0762 mmol, 27.1 % yield) as a yellow/orange powder. MS APCI (+) m/z 355 (M+1) detected.

Example 76

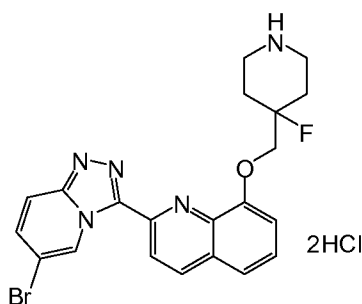


4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)pyrimidin-2-amine

[00608] Step A: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(2-chloropyrimidin-4-yloxy)quinoline: Prepared as described in Example 23 using 2,4-dichloropyrimidine in place of neopentyl iodide. MS APCI (+) m/z 375 (M+1) detected.

[00609] Step B: Preparation of 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-pyrimidin-2-amine: Prepared as described in Example 75, Step B, using 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(2-chloropyrimidin-4-yloxy)quinoline in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(2-chloropyridin-4-yloxy)quinoline. MS APCI (+) m/z 356 (M+1) detected.

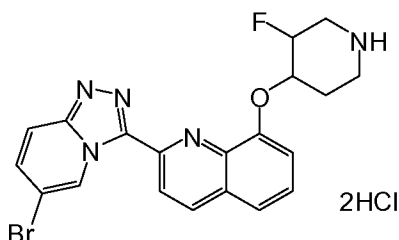
Example 77



2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)-quinoline dihydrochloride

[00610] Prepared as described in Example 66 using 2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in Step C. MS APCI (+) m/z 456/458 (M+1) (Br isotope) detected.

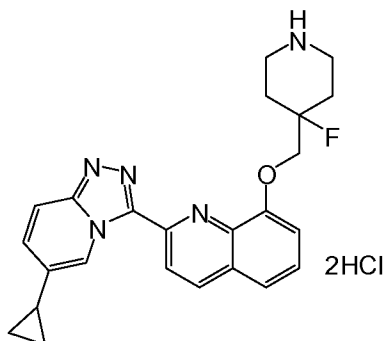
Example 78



2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline dihydrochloride

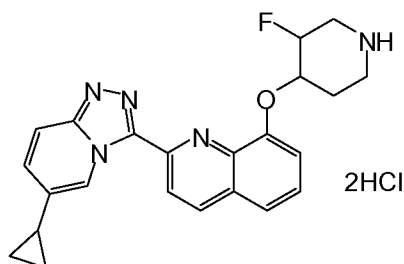
[00611] Prepared as described in Example 66 using (trans)-*tert*-butyl-3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate in place of *tert*-butyl 4-fluoro-4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate and 2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in Step C. MS APCI (+) m/z 442/444 (M+1) (Br isotope) detected.

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Example 79

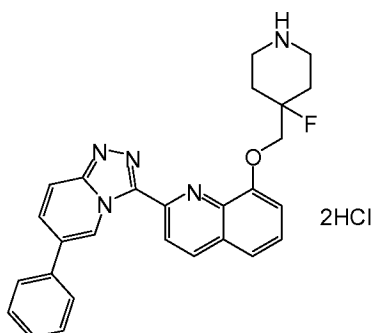
2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline dihydrochloride

[00612] Prepared as described in Example 66 using 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol. MS APCI (+) m/z 418 (M+1) detected.

Example 80

2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yl)oxyquinoline dihydrochloride

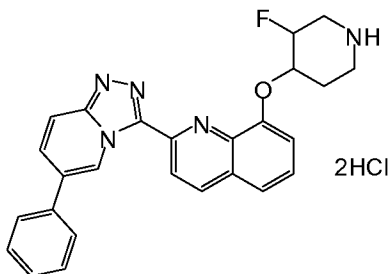
[00613] Prepared as described in Example 66 using 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol and (trans)-*tert*-butyl-3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate in place of *tert*-butyl 4-fluoro-4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate in Step C. MS APCI (+) m/z 404 (M+1) detected.

Example 81

8-((4-fluoropiperidin-4-yl)methoxy)-2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline dihydrochloride

[00614] Prepared as described in Example 66 using 2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in Step C. MS APCI (+) m/z 454 (M+1) detected.

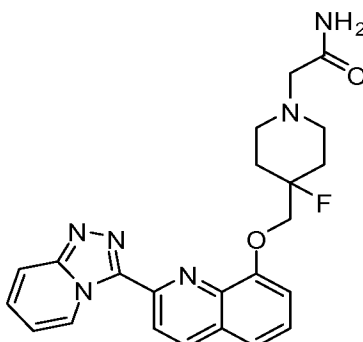
Example 82



8-((cis)-3-fluoropiperidin-4-yloxy)-2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline dihydrochloride

[00615] Prepared as described in Example 66 using 2-(6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol and (trans)-*tert*-butyl-3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate in place of *tert*-butyl 4-fluoro-4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate in Step C. MS APCI (+) m/z 440 (M+1) detected.

Example 83

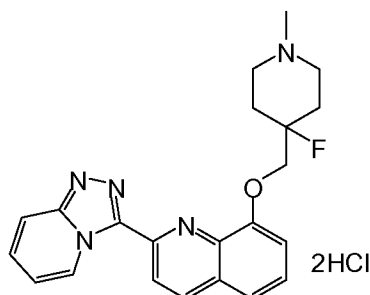


2-(4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-fluoropiperidin-1-yl)acetamide

[00616] To a suspension of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline dihydrochloride (0.050 g, 0.111 mmol) and TEA (0.0619 mL, 0.444 mmol) in 0.4 mL THF, 0.3 mL dichloromethane, and 0.2 mL DMF was added 2-bromoacetamide (0.0184 g, 0.133 mmol). The reaction mixture was heated in a 40 °C reaction block and stirred 1 hour. The reaction mixture was cooled to ambient temperature,

several drops of saturated NaHCO_3 were added, and the milky mixture was heated back to 40 °C and stirred another 3 hours. The reaction mixture was cooled to ambient temperature, diluted with water, and the resulting solids were collected by vacuum filtration through a 0.2 micron nylon filter disc, rinsed with water, air dried, then washed successively with ethyl acetate, dichloromethane, and ether, air dried, and dried in vacuo to give the title compound (0.014 g, 0.0322 mmol, 29.0 % yield) as a white powder. MS APCI (+) m/z 435 (M+1) detected.

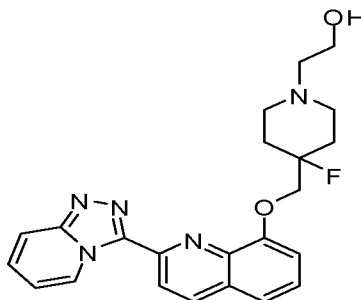
Example 84



2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoro-1-methylpiperidin-4-yl)methoxy)quinoline dihydrochloride

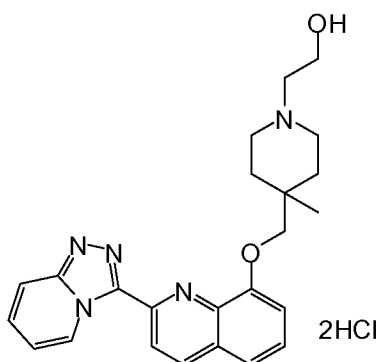
[00617] To a suspension of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline dihydrochloride (0.050 g, 0.111 mmol) and triethylamine (0.0619 mL, 0.444 mmol) in 0.6 mL DCE and 0.3 mL DMF was added 37% formaldehyde in water (0.0413 mL, 0.555 mmol). After stirring at ambient temperature for 15 minutes, $\text{Na}(\text{OAc})_3\text{BH}$ (0.0471 g, 0.222 mmol) was added, and the reaction mixture was stirred at ambient temperature for 18 hours. Another 10 equivalents of 37% formaldehyde was added, followed by 10 equivalents of $\text{Na}(\text{OAc})_3\text{BH}$. The reaction mixture was stirred another 6 hours, and saturated NaHCO_3 was added. The mixture was extracted with dichloromethane, and the combined extracts were dried (Na_2SO_4), filtered, and concentrated. The crude was purified by preparative TLC (1 mm plate, 6:1 dichloromethane: 6% NH_4OH in methanol). The resulting residue was dissolved in minimal dichloromethane, and this solution was added to a vigorously stirring solution of 1.5 mL 2M HCl/ether in 15 mL ether, causing precipitation. The solids were isolated by filtration through a medium glass fritted funnel by pushing the solvent through the frit with nitrogen pressure, rinsed with ether, dried under nitrogen pressure, and dried in vacuo to give the title compound (0.015 g, 0.0323 mmol, 29.1 % yield) as a white powder. MS APCI (+) m/z 392 (M+1) detected.

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Example 85

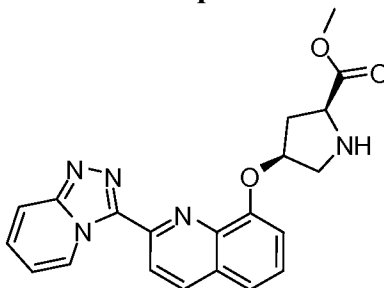
2-(4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-fluoropiperidin-1-yl)ethanol dihydrochloride

[00618] Prepared as described in Example 84 using 2-hydroxyacetaldehyde in place of 37% formaldehyde. MS APCI (+) m/z 422 (M+1) detected.

Example 86

2-(4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-fluoropiperidin-1-yl)ethanol dihydrochloride

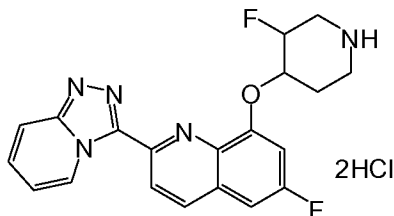
[00619] Prepared as described in Example 84 using 2-hydroxyacetaldehyde in place of 37% formaldehyde and 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-methylpiperidin-4-yl)methoxy)quinoline dihydrochloride in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline dihydrochloride. MS APCI (+) m/z 418 (M+1) detected.

Example 87

(2S,4S)-methyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)pyrrolidine-2-carboxylate

[00620] Prepared as described in Example 36 using (2S,4R)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate in place (2S,4S)-1-tert-butyl 2-methyl 4-hydroxypiperidine-1,2-dicarboxylate. MS ESI (+) m/z 390.1 (M+1) detected.

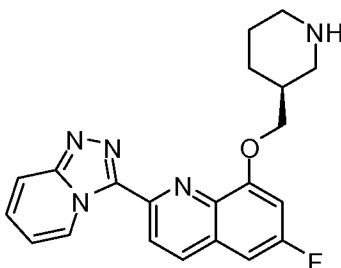
Example 88



2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline

[00621] Prepared as described in Example 26 using 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-quinolin-8-ol. MS ESI (+) m/z 382.2 (M+1) detected.

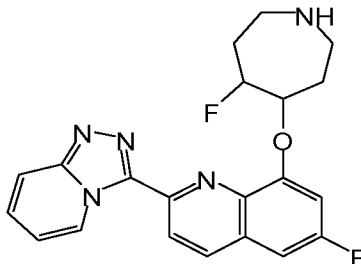
Example 89



(S)-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-(piperidin-3-ylmethoxy)quinoline

[00622] Prepared as described in Example 16 using (S)-tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate in place of tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate, and 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-quinolin-8-ol. MS ESI (+) m/z 378.2 (M+1) detected.

Example 90



Enantiomer 1 of cis-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-5-fluoroazepan-4-yloxy)quinoline

[00623] Step A: Preparation of *trans-tert*-butyl 4-fluoro-5-hydroxyazepane-1-carboxylate: To a *tert*-butyl 4-fluoro-5-oxoazepane-1-carboxylate (20.0 g, 86.5 mmol) was dissolved in THF (430 mL) solution and the solution was cooled to -5 °C. L-selectride (112 mL, 112 mmol, 1.0 M in THF) was added via syringe. The mixture was gradually warmed to ambient temperature over 3 hours and stirred for an additional 20 hours. The resulting cloudy mixture was diluted with 110 mL of MeOH which was followed by the addition of NaOH (355 mL, 355 mmol, 1.0M aqueous). The mixture was cooled in a water bath, and H₂O₂ (80.4 mL, 709 mmol, 30% aqueous) was added carefully via addition funnel over 30 minutes. The mixture was stirred vigorously for 1 hour, then diluted with water and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with water and 1N KHSO₄ (2 x 150 mL), and the combined aqueous phases were back-extracted with EtOAc (200 mL). The combined organic layers were washed with saturated aqueous NaHCO₃, then dried over Na₂SO₄, filtered and concentrated. The crude product was purified via column chromatography (15% to 60% EtOAc/hexanes) to provide the product as a thick colorless oil which slowly became a white solid (13.9 g, 69%; diastereomeric ratio (dr): ~7:1 *trans*:*cis*).

[00624] Step B: Preparation of *trans-tert*-butyl 4-fluoro-5-(4-nitrophenylsulfonyloxy)azepane-1-carboxylate: *trans-tert*-butyl 4-fluoro-5-hydroxyazepane-1-carboxylate (12.36 g, 52.98 mmol) was dissolved in CH₂Cl₂ (110 mL). The solution was cooled to 0 °C, 4-nitrobenzene-1-sulfonyl chloride (14.09 g, 63.58 mmol) was added and the mixture was stirred for 10 minutes. NEt₃ (11.08 mL, 79.48 mmol) was added and the mixture was slowly warmed to ambient temperature over 1 hour and stirred for an additional 2 hours. The mixture was diluted with CH₂Cl₂ and washed with water followed by 1N KHSO₄ (2 x 50 mL), then with saturated aqueous NaHCO₃ (50 mL) and brine, and the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified via column chromatography (10 to 70% MTBE/hexanes) to provide 18.4 g of the product (84 %) as a single isomer and as a faint orange powder.

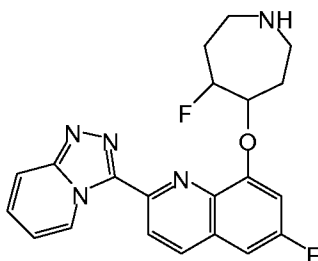
[00625] Step C: Preparation of *cis-tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-5-fluoroazepane-1-carboxylate: *trans-tert*-Butyl 4-fluoro-5-(4-nitrophenylsulfonyloxy)azepane-1-carboxylate (0.526 g, 1.26 mmol) and 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol (0.320 g, 1.14 mmol) were slurried in CH₃CN (5.5 mL). To this mixture was added 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (0.276 mL, 1.37 mmol) dropwise. The mixture was warmed to 40 °C and stirred overnight.

The mixture was cooled to ambient temperature and diluted with water (10 mL) and stirred for 15 minutes, then filtered, and the solid was washed with water and hexanes and dried. This provided 0.460 g of the title compound (81%) as an off-white solid (>95% pure by HPLC). MS ESI (+) m/z 496.0 (M+1) detected.

[00626] Step D: Isolation of Enantiomer 1 of *cis*-tert-butyl 4-(2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-5-fluoroazepane-1-carboxylate: Racemic *cis*-tert-butyl 4-(2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-5-fluoroazepane-1-carboxylate was separated by chiral HPLC on a Prep Chiral OJ-H column using the following solvent mixture: 75% heptane, 20% EtOH, 3% MeOH, 2% acetonitrile, to provide the enantiomers as peak 1 (7.573 minutes) and peak 2 (8.373 minutes). Peak 1 was isolated to provide the title compound 99% ee, 99% de. MS ESI (+) m/z 496.0 (M+1) detected.

[00627] Step E: Preparation of Enantiomer 1 of *cis*-2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-6-fluoro-8-5-fluoroazepan-4-yloxy)quinoline: Enantiomer 1 of *cis*-tert-butyl 4-(2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-5-fluoroazepane-1-carboxylate (0.119 g, 0.240 mmol) was dissolved in CHCl₃ (2.4 mL). HCl (2.40 mL, 9.61 mmol, 4.0 M dioxane) was added and the mixture was stirred at ambient temperature for 3 hours. The mixture was filtered through a polypropylene filter and washed with CH₂Cl₂ and Et₂O, then slurried in hexanes and dried carefully *in vacuo* to provide 0.095 g of the desired product as a white solid (85%). MS ESI (+) m/z 396.1 (M+1) detected. Specific rotation: $[\alpha]_D^{25} = -49.6^\circ$ ($c = 0.95$, MeOH).

Example 91



Enantiomer 2 of *trans*-2-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-6-fluoro-8-5-fluoroazepan-4-yloxy)quinoline

[00628] Step A: Preparation of *trans*-tert-butyl 4-fluoro-5-hydroxyazepane-1-carboxylate: To a tert-butyl 4-fluoro-5-oxoazepane-1-carboxylate (20.0 g, 86.5 mmol) was dissolved in THF (430 mL) solution and the solution was cooled to -5 °C. L-Selectride (112 mL, 112 mmol, 1.0 M in THF) was added via syringe. The mixture was gradually warmed to ambient temperature over 3 hours and stirred for an additional 20 hours. The resulting cloudy

mixture was diluted with 110 mL of MeOH, followed by addition of NaOH (355 mL, 355 mmol, 1.0M aqueous). The mixture was cooled in a water bath and H₂O₂ (80.4 mL, 709 mmol, 30% aqueous) was added carefully via addition funnel over 30 minutes. The mixture was stirred vigorously for 1 hour. The mixture was diluted with water and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with water and 1N KHSO₄ (2 x 150 mL), and the combined aqueous phases were back extracted with EtOAc (200 mL). The combined organic layers were washed with saturated aqueous NaHCO₃, dried over Na₂SO₄, filtered and concentrated. The crude product was purified via column chromatography (15% to 60% EtOAc/hexanes) to provide the product as a thick colorless oil which slowly became a white solid (13.9g, 69%; diastereomeric ratio (dr): ~7:1 *trans*:*cis*).

[00629] Step B: Preparation of *cis*-*tert*-butyl 4-fluoro-5-hydroxyazepane-1-carboxylate: *trans*-*tert*-butyl 4-fluoro-5-hydroxyazepane-1-carboxylate (25.00 g, 107.2 mmol) was dissolved in THF (1100 mL). To this solution was added 2-chloroacetic acid (15.19 g, 160.8 mmol) and PPh₃ (42.16 g, 160.8 mmol). The solution was cooled to 0 °C and DEAD (25.31 mL, 160.8 mmol) was added as a THF solution (250 mL). The reaction mixture was protected from light and stirred overnight as it slowly increased to ambient temperature. The THF was removed *in vacuo* and replaced with EtOAc. The solution was washed with saturated aqueous NaHCO₃, dried over Na₂SO₄, filtered and concentrated. The crude product was dissolved in dioxane (500 mL), and water was added (250 mL). A 1N NaOH solution was added until the pH reached ~10 (200 mL). The mixture was stirred for 1 hour and then quenched with 1N KHSO₄ (250 mL). The mixture was extracted with EtOAc (3 x 250 mL) and the combined organic phases were washed with saturated aqueous NaHCO₃, dried over Na₂CO₃, filtered and concentrated to a white paste. The paste was then slurried in 50% Et₂O/hexanes (200 mL) and filtered through qualitative paper. The resulting white solid was washed with 50% Et₂O/hexanes (3 x 200 mL) and the filtrate was concentrated. The crude residue was purified by column chromatography (10 to 40% Acetone/hexanes) to provide the product (22.4 g, 89%) as a thick colorless oil.

[00630] Step C: Preparation of *cis*-*tert*-butyl 4-fluoro-5-(4-nitrophenylsulfonyloxy)azepane-1-carboxylate: *cis*-*tert*-butyl 4-fluoro-5-hydroxyazepane-1-carboxylate (22.3 g, 95.59 mmol) was dissolved in CH₂Cl₂ (240 mL). The solution was cooled to 0 °C, 4-nitrobenzene-1-sulfonyl chloride (25.42 g, 114.7 mmol) was added and the mixture was stirred for 30 minutes. NEt₃ (19.99 mL, 143.4 mmol) was added and the mixture was slowly warmed to ambient temperature over 2 hours and stirred overnight. The mixture

was diluted with CH₂Cl₂ and washed with 1N KHSO₄ (2 x 100 mL) followed by washing with saturated aqueous NaHCO₃ (100 mL) and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude orange solid was dissolved in minimal hot CH₂Cl₂ and hexanes were added with stirring until the solution became persistently cloudy. The warm mixture was cooled to ambient temperature and allowed to stand undisturbed for 1 hour. The solids were collected by filtration and the solid was successively washed with hexanes followed by 50% Et₂O/hexanes and finally with hexanes again to provide the clean *cis* isomer of the product as a pale yellow solid (27.05 g, 68%).

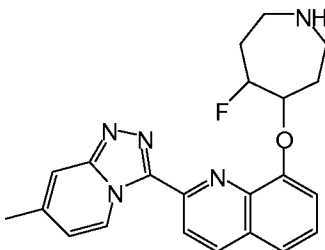
[00631] Step D: Preparation of *trans-tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-5-fluoroazepane-1-carboxylate: *cis-tert*-butyl 4-fluoro-5-(4-nitrophenylsulfonyloxy)azepane-1-carboxylate (0.484 g, 1.16 mmol) and 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol (0.300 g, 1.07 mmol) were slurried in CH₃CN (5.0 mL). To this mixture was added 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (0.259 mL, 1.28 mmol) dropwise. The dark solution was warmed to 40 °C and stirred overnight. The mixture was cooled to ambient temperature and diluted with water (10 mL) and stirred for 15 minutes, then filtered. The solid was washed with water and hexanes and dried *in vacuo*. The product was purified via column chromatography (10 to 50% Acetone/CH₂Cl₂) to provide the product as off-white solid. MS ESI (+) *m/z* 496.0 (M+1) detected.

[00632] Step E: Isolation of Enantiomer 2 of *trans-tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-5-fluoroazepane-1-carboxylate: Racemic *trans tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-5-fluoroazepane-1-carboxylate was separated by chiral HPLC on a Prep Chiral OJ-H column using the following solvent system: 20% EtOH and 80% hexanes, to provide the two enantiomers as peak 1 (9.715 minutes) and peak 2 (14.265 minutes). Peak 2 was isolated to provide the title compound with 98% ee and 99% de.

[00633] Step F: Enantiomer 2 of *trans*-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-5-fluoroazepan-4-yloxy)quinoline: Enantiomer 2 of *trans-tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-5-fluoroazepane-1-carboxylate (0.210 g, 0.424 mmol) was dissolved in CHCl₃ (4.3 mL). To this solution was added HCl (4.24 mL, 17.0 mmol, 4.0M Dioxane) and the mixture was stirred at ambient temperature for 3 hours. The mixture was filtered through a polypropylene filter and washed with CH₂Cl₂ and Et₂O, then slurried in hexanes and dried *in vacuo* to provide the desired product as white

solid. MS ESI (+) m/z 396.1 (M+1) detected. Specific rotation: $[\alpha]_D^{25} = -77^\circ$ ($c = 0.95$, MeOH).

Example 92



Enantiomer 1 of *cis*-8-(5-fluoroazepan-4-yloxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline

[00634] Step A: Preparation of 2-hydrazinyl-4-methylpyridine: 2-Chloro-4-methylpyridine (3.43 mL, 39.19 mmol) and hydrazine hydrate (19.07 mL, 391.9 mmol) were suspended together in a flask and heated to 150 °C for 72 hours. The mixture was concentrated *in vacuo* to an oil. The oil was taken up in EtOAc and the resulting solid was removed by vacuum filtration. The organic filtrate was washed with 40% aqueous NaOH (2 x 50 mL) and dried over Na₂SO₄, filtered and concentrated to provide the desired product (2.42 g, 54%) as a white solid.

[00635] Step B: Preparation of (*E*)-8-(*tert*-butyldimethylsilyloxy)-2-((2-(4-methylpyridin-2-yl)hydrazono)methyl)quinoline: 2-Hydrazinyl-4-methylpyridine (0.280 g, 2.27 mmol) and 8-(*tert*-butyldimethylsilyloxy)quinoline-2-carbaldehyde (0.653 g, 2.27 mmol) were suspended in EtOH (6 mL) and stirred overnight at ambient temperature. The resulting suspension was filtered and the solid was washed with cold EtOH and dried *in vacuo* to provide the title compound (0.720 g ; 81 %).

[00636] Step C: Preparation of 8-(*tert*-butyldimethylsilyloxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline: (*E*)-8-(*tert*-Butyldimethylsilyloxy)-2-((2-(4-methylpyridin-2-yl)hydrazono)methyl)quinoline (0.720 g, 1.83 mmol) was suspended in DCM (6 mL) at ambient temperature. Iodobenzene diacetate (0.650 g, 2.02 mmol) was added and the solution was allowed to stir at ambient temperature overnight. The mixture was concentrated to an orange oil and purified directly by column chromatography (20% EtOAc/DCM to 50% EtOAc/DCM) to provide the desired product (0.590 g, 82%).

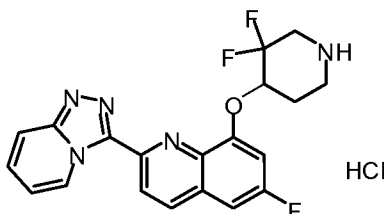
[00637] Step D: Preparation of 2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol. 8-(*tert*-butyldimethylsilyloxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline (0.580 g, 1.49 mmol) was suspended in THF (2 mL) and the solution was cooled to 0 °C.

Tetrabutylammonium fluoride hydrate (0.582 g, 2.23 mmol) was added to the solution and the mixture stirred at 0 °C for 10 minutes, then warmed to ambient temperature and stirred for 4 hours. The mixture was diluted with a saturated aqueous NH₄Cl solution and EtOAc. The resulting white solid was isolated by vacuum filtration and was combined with the organic layer which was concentrated. The solid thus obtained was slurried in H₂O for 10 minutes and the solids isolated by vacuum filtration and dried to provide the title compound (0.320 g, 78%) as a white solid. MS ESI (+) *m/z* 277.1 (M+1) detected.

[00638] Step E: Preparation of *cis*-*tert*-butyl 4-fluoro-5-(2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)azepane-1-carboxylate: 2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (300 mg, 1.09 mmol) was suspended in CH₃CN (5 mL) at ambient temperature, and *trans-tert*-butyl 4-fluoro-5-(4-nitrophenylsulfonyloxy)azepane-1-carboxylate (454 mg, 1.09 mmol) and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (263 μL, 1.30 mmol) were added. The dark solution was stirred at 40 °C overnight, then concentrated to a grey solid which was slurried in water for 10 minutes. The solid was filtered, washed and dried *in vacuo* to provide the desired product. MS ESI (+) *m/z* 492.3 (M+1) detected.

[00639] Step F: Isolation of Enantiomer 1 of *cis*-*tert*-butyl 4-fluoro-5-(2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)azepane-1-carboxylate: Racemic *cis*-*tert*-butyl 4-fluoro-5-(2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)azepane-1-carboxylate was separated by chiral HPLC on a Prep Chiral OJ-H column using the following solvent system: 90% hexanes, 10% EtOH, to provide the two enantiomers as peak 1 (7.397 minutes) and peak 2 (10.335 minutes). Peak 1 was collected to provide the title compound with 99% ee, 99% de.

[00640] Step G: Enantiomer 1 of *cis*-8-5-fluoroazepan-4-yloxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline: Enantiomer 1 of *cis-tert*-butyl 4-fluoro-5-(2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)azepane-1-carboxylate (0.161 g, 0.328 mmol) was dissolved in CHCl₃ (3 mL). To this solution was added HCl (6.55 mL, 13.1 mmol, 2.0M Et₂O) and the mixture was stirred at ambient temperature for 4 hours. The mixture was filtered through a polypropylene filter, washed with CH₂Cl₂ and Et₂O, slurried in hexanes, then dried carefully *in vacuo* to provide the desired product as a white solid. MS ESI (+) *m/z* 392.1 (M+1) detected. Specific rotation: $[\alpha]_D^{25} = -50^\circ$ (c = 1.0, MeOH).

Example 93

2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(3,3-difluoropiperidin-4-yloxy)-6-fluoroquinoline dihydrochloride

[00641] Step 1A: Preparation of N-(2,4-difluorophenyl)cinnamamide: 2,4-difluoroaniline (9.0 g, 69.71 mmol) and pyridine (5.6 mL, 69.71 mmol) were dissolved in dichloromethane (45 mL) and the solution was cooled to 0 °C. A solution of cinnamoyl chloride (13.04 g, 76.7 mmol) dissolved in dichloromethane (45 mL) was added dropwise, and after the addition the reaction was warmed to ambient temperature and stirred for 16 hours. The reaction was quenched with saturated NaHCO₃ and the layers were separated. The organic layer was washed with 1 M HCl then dried over Na₂SO₄ and concentrated in vacuo to provide a white solid. The solid was slurried in dichloromethane (150 mL), stirred for 30 minutes, and then hexanes (150 mL) were added. After stirring several minutes, the white solids were collected by filtration, washed with dichloromethane and air-dried to provide 13.5 g of the desired product. MS APCI (-) *m/z* 258.0 (M-1) detected.

[00642] Step 1B: Preparation of 6,8-difluoroquinolin-2-ol: Solid N-(2,4-difluorophenyl)cinnamamide (13.2 g, 50.7 mmol) was pre-mixed with aluminum trichloride (20.29 g, 152.2 mmol) and the mixture was heated to 160 °C under gently flowing nitrogen gas for 80 minutes. The reaction was cooled and quenched with ice, and the resultant beige solid was collected by filtration, washed with water and air-dried to a light tan solid (9.89 g).

[00643] Step 1C: Preparation of 2-chloro-6,8-difluoroquinoline: 6,8-Difluoroquinolin-2-ol (9.89 g, 54.6 mmol) was slurried in 1,2-dichloroethane (550 mL) and treated with DMF (1 mL), and then 2M oxalyl chloride in CH₂Cl₂ (81.9 mL, 164 mmol) was added dropwise. The reaction was heated to 70 °C for 1 hour and then cooled and concentrated in vacuo. The residue was dissolved in CHCl₃ and washed with 50% saturated NaHCO₃. The aqueous layer (pH 8) was washed twice with CHCl₃ and the combined organics were dried over Na₂SO₄ and charcoal, filtered, and concentrated in vacuo to a brown solid. The solid was purified by recrystallization from hot hexanes and 1,2-dichloroethane (minimum volume). The solid was collected, washed with hexanes and air-dried to provide the desired product as an off-white solid (5.78 g).

[00644] Step 2: Preparation of [1,2,4]triazolo[4,3-a]pyridine: 2-Hydrazinylpyridine (5.06 g, 46.4 mmol) was treated with triethoxymethane (50.2 mL, 302 mmol) and the mixture was heated to reflux for 4 hours with nitrogen flowing over the top of the air condenser. The air condenser was replaced with a small distillation head and the low boiling solvents (75-80 °C) were removed from the system. Heating continued for 16 hours. The reaction was cooled to ambient temperature and concentrated in vacuo to a dark residue. The residue was chromatographed on SiO₂ eluting with a gradient of 6% NH₄OH in MeOH/ethyl acetate. The desired product was isolated as a light orange solid (4.2 g). MS APCI (+) *m/z* 120.0 (M+1) detected.

[00645] Step 3: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6,8-difluoroquinoline: 2-Chloro-6,8-difluoroquinoline (0.025 g, 0.125 mmol) was combined with [1,2,4]triazolo[4,3-a]pyridine (0.016 g, 0.14 mmol), micronized Cs₂CO₃ (0.082 g, 0.25 mmol), and PdCl₂(PPh₃)₂ (0.0088 g, 0.013 mmol), and the solids were slurried in dioxane (1.25 mL). The reaction was degassed with argon (bubbled through the solution) then heated to reflux for 20 hours. The crude reaction mixture was chromatographed without workup on SiO₂ eluting with a gradient of 6% NH₄OH in MeOH/ethyl acetate to provide the desired product as an orange solid (21 mg).

[00646] Step 4A: Preparation of 1-benzyl-3,3-difluoropiperidine-4,4-diol: Ethyl 1-benzyl-5,5-difluoro-4-oxopiperidine-3-carboxylate (6.00 g, 20.2 mmol; prepared as described in WO 2005/040120, p. 30) was dissolved in 3N HCl (60 mL) and heated to reflux for 16 hours. The reaction was cooled, adjusted to pH 8 with solid NaHCO₃, then extracted three times with ethyl acetate. The combined organics were washed with saturated NaCl, dried over Na₂SO₄ and concentrated in vacuo to a white solid (5.1 g). MS APCI (+) *m/z* 244.0 (M+1) detected.

[00647] Step 4B: Preparation of tert-butyl 3,3-difluoro-4,4-dihydroxypiperidine-1-carboxylate: 1-Benzyl-3,3-difluoropiperidine-4,4-diol (2.05 g, 8.43 mmol) was dissolved in 95% EtOH (40 mL) and treated with di-tert-butyl dicarbonate (3.68 g, 16.9 mmol) and 10% Pd on carbon (Degeussa type, 200 mg). The reaction was placed under a balloon of hydrogen gas and stirred for 12 hours. The reaction mixture was filtered through a nylon membrane, washed with ethanol and concentrated in vacuo to a colorless oil (4.05 g).

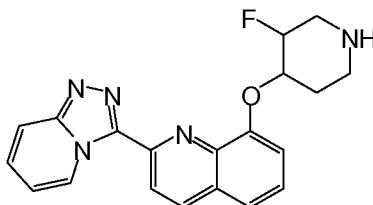
[00648] Step 4C: Preparation of tert-butyl 3,3-difluoro-4-hydroxypiperidine-1-carboxylate: tert-Butyl 3,3-difluoro-4,4-dihydroxypiperidine-1-carboxylate (3.10 g, 12.2 mmol) was dissolved in 95% EtOH (50 mL) and the solution was treated with sodium

borohydride (2.32 g, 61.2 mmol) and stirred at ambient temperature for 3 hours. The reaction was treated dropwise with 3N HCl until vigorous gas evolution ceased, then stirred at ambient temperature for 20 minutes (pH of the mixture was 3-4 at this point). The reaction was neutralized with saturated NaHCO₃ and concentrated in vacuo. The residue was dissolved in ethyl acetate and water and the layers were separated. The aqueous layer was washed with ethyl acetate and the combined organic layers were washed with saturated NaCl, dried over Na₂SO₄ and concentrated in vacuo to provide the desired product as a white solid (1.39 g).

[00649] Step 5A: Preparation of tert-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-3,3-difluoropiperidine-1-carboxylate: tert-Butyl 3,3-difluoro-4-hydroxypiperidine-1-carboxylate (0.0706 g, 0.298 mmol) was treated with 1 M KOtBu in THF (0.283 mL, 0.283 mmol) and stirred for 15 minutes. The solution was treated with 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6,8-difluoroquinoline (0.042 g, 0.149 mmol) and DMF (0.80 mL) then the mixture was stirred at ambient temperature for 16 hours. The mixture was directly chromatographed on SiO₂ eluting with a gradient of 2% NH₄OH in isopropanol/ethyl acetate. The desired product was collected and concentrated to a colorless oil, (72 mg). MS APCI (+) *m/z* 500.0 (M+1) detected.

[00650] Step 5B: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(3,3-difluoropiperidin-4-yloxy)-6-fluoroquinoline dihydrochloride salt: tert-Butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-3,3-difluoropiperidine-1-carboxylate (0.072 g, 0.144 mmol) was dissolved in MeOH (0.72 mL) and treated with 4.0 M HCl in dioxane (0.360 mL, 1.44 mmol), then stirred at ambient temperature for 2 hours. The reaction mixture was concentrated in vacuo. The residue was taken up in MeOH and concentrated three times. The residue was chromatographed on SiO₂ eluting with a gradient of 2% NH₄OH in isopropanol/methylene chloride. The desired product was dissolved in MeOH (2 mL), treated with 2.0 M HCl in ether (0.809 mL, 1.62 mmol) and concentrated in vacuo. The residue was again dissolve in MeOH and concentrated in vacuo several times, then placed under vacuum to give the desired product as a white solid (27.8 mg). MS APCI (+) *m/z* 400.3 (M+1) detected.

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Example 94

Enantiomer 1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline dihydrochloride

[00651] Step 1A: Preparation of N-(2-fluorophenyl)cinnamamide: Cinnamoyl chloride (89.2 g, 535 mmol) was dissolved in THF (170 mL) and added dropwise to a 0 °C solution of 2-fluoroaniline (54.1 g, 486 mmol) and pyridine (39.35 mL, 486.5 mmol) dissolved in THF (170 mL). The mixture was allowed to warm to ambient temperature after the addition and stirred for 15 hours. A solution of 2M HCl was added (1250 mL) and the mixture was stirred at ambient temperature for 8 hours, during which the initial oil solidified to a light pink solid. This material was collected by filtration, washed with several portions of water, and air-dried to provide the desired product (119.5 g).

[00652] Step 1B: Preparation of 8-fluoroquinolin-2-ol: N-(2-Fluorophenyl)cinnamamide (97.2 g, 403 mmol) was combined with AlCl₃ (161 g, 1209 mmol) and the solids were thoroughly mixed. The dry mixture was heated to 160 °C for 100 minutes. The reaction was cooled and quenched by addition of ice. A beige solid formed after complete dispersion of the dark solids and this was stirred overnight. The beige solid was filtered and air-dried overnight to provide the desired product as a free-flowing solid (69.8 g).

[00653] Step 1C: Preparation of 2-chloro-8-fluoroquinoline: 8-Fluoroquinolin-2-ol (35 g, 215 mmol) was slurried in 1,2-dichloroethane (875 mL) and treated with DMF (3 mL) then a solution of oxalyl chloride (2M in CH₂Cl₂) (322 mL, 644 mmol) was added dropwise. After the addition, the reaction was heated to 70 °C for 1 hour then cooled and concentrated in vacuo. The residue was dissolved in CHCl₃ and washed with 50% saturated NaHCO₃. The aqueous layer (pH 8) was washed twice with CHCl₃ and the combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to a brown solid (about 52 g). This crude solid was dissolved in methylene chloride and filtered through a plug of SiO₂ eluting with methylene chloride. The desired material was isolated as a light orange solid (32.9 g).

[00654] Step 2: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-fluoroquinoline: 2-Chloro-8-fluoroquinoline (0.75 g, 4.13 mmol) was combined with [1,2,4]triazolo[4,3-

a]pyridine (0.541 g, 4.54 mmol), micronized Cs_2CO_3 (2.69 g, 8.26 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.290 g, 0.413 mmol) then the mixture was slurried in dioxane (20 mL). The reaction was deoxygenated with argon and heated to reflux for 20 hours, then cooled, diluted with CHCl_3 and filtered through a pad of Celite®. The filtrate was concentrated onto Na_2SO_4 powder (15 g) and the mixture was chromatographed on SiO_2 eluting with a stepped gradient of 0-2% MeOH / ethyl acetate. The desired product was isolated as a cream-colored solid (1.12 g). MS APCI (+) m/z 265.3 (M+1) detected.

[00655] Step 3A: Preparation of benzyl 4-(trimethylsilyloxy)-5,6-dihydropyridine-1(2H)-carboxylate: To benzyl 4-oxopiperidine-1-carboxylate (152 g, 650 mmol) in DMF (650 mL) was added TMS-Cl (148 mL, 117 mmol) followed by triethylamine (326 mL, 234 mmol). The slurry was warmed to 80 °C for 16 hours, diluted with hexanes (1 L), washed 3 times with saturated NaHCO_3 solution, dried over Na_2SO_4 , filtered and concentrated to obtain benzyl 4-(trimethylsilyloxy)-5,6-dihydropyridine-1(2H)-carboxylate, (199 g, 652 mmol) as a orange oil.

[00656] Step 3B: Preparation of benzyl 3-fluoro-4-oxopiperidine-1-carboxylate: Selectfluor® (181.2 g, 511.4 mmol) was added portion-wise (about 25 g portions) to a ice cold solution of benzyl 4-(trimethylsilyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (142 g, 465 mmol) in CH_3CN (2 L) over approximately 30 minutes. The ice bath was removed and the mixture was allowed to stand for 12 hours. The mixture was concentrated to a slurry, diluted with EtOAc and brine and the layers were separated. The brine phase was extracted once with EtOAc, and the combined organic phases were washed with saturated NaHCO_3 and brine, dried over Na_2SO_4 , filtered and concentrated in vacuo to provide the desired product as a dark thick oil (112 g).

[00657] Step 3C: Preparation of cis-benzyl 3-fluoro-4-hydroxypiperidine-1-carboxylate: L-Selectride® (663 mL, 663 mmol) was added dropwise to an ice cold solution of benzyl 3-fluoro-4-oxopiperidine-1-carboxylate (138.9 g, 552.8 mmol) dissolved in anhydrous THF (421 mL). The ice bath was removed and the reaction was allowed to stand for 12 hours. The reaction mixture was carefully added (dropwise, via addition funnel) to a vigorously stirring mixture of 80 mL MeOH, 2 N NaOH (1400 mL) H_2O_2 (376 mL, 50 %) in a large amount of ice, taking care to control the temperature rise. The mixture was stirred for 12 hours, then 2 L of EtOAc was added. The mixture was stirred an additional 1 hour. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 , filtered and concentrated in vacuo to an oil (112 g).

The residue was purified by flash column chromatography (silica gel, eluting with a gradient of 30 % EtOAc to 75 % EtOAc in hexanes) to afford 38 g of the desired compound.

[00658] Step 3D: Preparation of non-racemic cis-benzyl 3-fluoro-4-hydroxypiperidine-1-carboxylate: A 32 g sample of the material of Step 3C was separated by chiral SFC separation (3 cm x 15 cm Chiralpak AD-H column; mobile phase 22% Ethanol/CO₂, 100 bar; flow rate 100 mL/min; 50 mg/mL injections, 1.5 mL injection volume; 220 nM) to afford first eluting peak (Peak 1; 11.2 g, Rt 2.63 min) in >99% ee and second eluting peak (Peak 2; 11.8 g, Rt 4.01 min) in >99% ee.

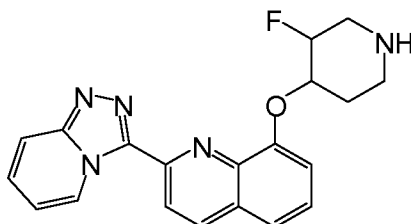
[00659] Step 4A: Preparation of Enantiomer 1 of (cis)-benzyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3-fluoropiperidine-1-carboxylate: Non-racemic (cis)-benzyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (Peak 1 of Example 94, Step 3D; 0.288 g, 1.14 mmol) was treated with 1.0 M KOtBu in THF (1.10 mL, 1.10 mmol) and stirred at ambient temperature for 15 minutes. 2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-8-fluoroquinoline (0.200 g, 0.757 mmol) was added as a solid, followed by the addition of DMF (3.3 mL), and the resultant mixture was stirred at ambient temperature for 40 hours. The crude reaction mixture was chromatographed on SiO₂ eluting with a gradient of (2% NH₄OH in isopropanol)/methylene chloride. The desired product was isolated as a pale yellow solid (196 mg). MS APCI (+) *m/z* 498.2 (M+1) detected.

[00660] Step 4B: Preparation of Enantiomer 1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline: Enantiomer 1 of (cis)-benzyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3-fluoropiperidine-1-carboxylate (0.185 g, 0.372 mmol) was dissolved in dioxane (4.6 mL) and treated with 6 M hydrogen chloride (4.65 mL, 27.9 mmol) and the reaction mixture was heated at 100 °C for 2 hours. The reaction was cooled and carefully neutralized with solid NaHCO₃. The resulting aqueous layer (pH 8-9) was extracted four times with methylene chloride and the resulting organic layers were combined and dried over Na₂SO₄ then concentrated in vacuo. The residue was chromatographed on SiO₂ eluting with a gradient of 6% NH₄OH in MeOH)/methylene chloride. The desired material was isolated as a colorless film (22 mg). MS APCI (+) *m/z* 364.1 (M+1) detected.

[00661] Step 4C: Preparation of the dihydrochloride salt of Enantiomer 1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline: Non-racemic 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline (20 mg, 0.055 mmol) was dissolved in MeOH (2 mL) and treated with 4M HCl in dioxane (1

mL, 4 mmol). The mixture was stirred for 5 minutes then concentrated in vacuo. The residue was dissolved in fresh MeOH and concentrated in vacuo three times to a pale yellow solid (20.7 mg, 86%). Specific rotation: $[\alpha]_D^{20} = +26^\circ$ (c = 0.45, 1:1 water/95% ethanol).

Example 95

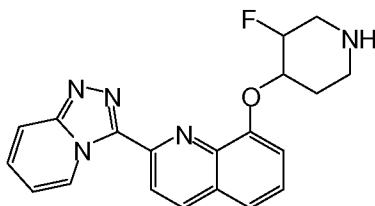


Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline dihydrochloride

[00662] Step 1: Preparation of Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline: Prepared according to the method of Example 94 using Peak 2 of non-racemic (cis)-benzyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (Example 94, Step 3D) in place of Peak 1 of non-racemic (cis)-benzyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (Example 94, Step 3D) in step 4A. MS APCI (+) m/z 364.1 (M+1) detected.

[00663] Step 2: Preparation of the dihydrochloride salt Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline: Prepared as described in Example 94 using non-racemic 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((cis)-3-fluoropiperidin-4-yloxy)quinoline in Step 4C. Specific rotation: $[\alpha]_D^{20} = -48^\circ$ (c = 0.46, 1:1 water / 95% ethanol).

Example 96



Enantiomer 1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline dihydrochloride

[00664] Step 1A: Preparation of Enantiomer 1 of (trans)-benzyl 4-(benzoyloxy)-3-fluoropiperidine-1-carboxylate: Non-racemic (cis)-benzyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (Peak 1 of Example 94, Step 3D; 0.306 g, 1.21 mmol) was treated with triphenylphosphine (0.475 g, 1.81 mmol) and benzoic acid (0.221 g, 1.81 mmol) and the

solids were dissolved in THF (5 mL), then cooled to 0 °C. The solution was treated dropwise with diisopropyl azodicarboxylate (0.357 mL, 1.81 mmol) dissolved in THF (1 mL). The solution was warmed to ambient temperature with a bath and stirred for 7 days, then concentrated in vacuo. The residue was dissolved in CH₂Cl₂ and washed with saturated NH₄Cl, water, 50% saturated NaHCO₃, dried over Na₂SO₄ and concentrated in vacuo to a colorless oil. The oil was chromatographed on SiO₂ eluting with 1:12 acetone/hexanes. The desired fraction was isolated to provide the desired product as a colorless oil (385 mg).

[00665] Step 1B: Preparation of Enantiomer 1 of (trans)-benzyl 3-fluoro-4-hydroxypiperidine-1-carboxylate: Enantiomer 1 of (trans)-benzyl 4-(benzyloxy)-3-fluoropiperidine-1-carboxylate (6.50 g, 18.2 mmol) was dissolved in THF/MeOH/water (2:2:1, 50 mL) and treated with lithium hydroxide hydrate (1.53 g, 36.4 mmol), and the reaction was stirred at 50 °C for 2 hours. The reaction mixture was cooled, quenched with saturated NH₄Cl to pH 8, concentrated in vacuo and the aqueous layer (pH 8) was extracted with methylene chloride. The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo to a colorless oil (295 mg). The crude material was chromatographed on SiO₂ eluting with 2:1 hexanes/ethyl acetate. The desired material was isolated as a colorless oil (3.7 g).

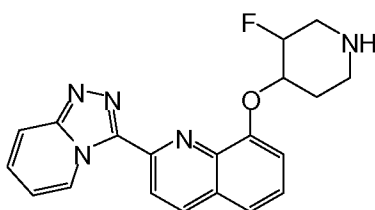
[00666] Step 2A: Preparation of Enantiomer 1 of (trans)-benzyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3-fluoropiperidine-1-carboxylate: Non-racemic (trans)-benzyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (0.192 g, 0.757 mmol) was treated with 1.0 M KOtBu in THF (0.757 mL, 0.757 mmol) and stirred at ambient temperature for 15 minutes. 2-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-8-fluoroquinoline (0.200 g, 0.757 mmol) was added along with DMF (2.25 mL) and the mixture was stirred at 50 °C for 15 hours. The reaction was cooled and chromatographed on SiO₂, eluting with a gradient of 2% NH₄OH in isopropanol/methylene chloride. After concentration in vacuo, the desired product was isolated as a beige solid (0.306 g). MS APCI (+) *m/z* 498.1 (M+1) detected.

[00667] Step 2B: Preparation of Enantiomer 1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline: Non-racemic (trans)-benzyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3-fluoropiperidine-1-carboxylate (0.304 g, 0.611 mmol) was dissolved in dioxane (7.6 mL) and treated with 6 M hydrogen chloride (7.64 mL, 45.8 mmol), and the reaction mixture was heated at 100 °C for 15 hours. The reaction was cooled and carefully neutralized with solid NaHCO₃. Additional water was added to dissolve the resulting NaCl as the neutralization proceeded. The resulting aqueous

layer (pH 8-9) was extracted with methylene chloride and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was chromatographed on SiO_2 eluting with a gradient of 2% NH_4OH in isopropanol/methylene chloride. The desired product was isolated as a white foam (62.6 mg). MS APCI (+) m/z 364.2 (M+1) detected.

[00668] Step 2C: Preparation of the dihydrochloride salt of Enantiomer 1 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline: Prepared as described in Example 94 using non-racemic 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline in Step 4C. Specific rotation: $[\alpha]_D^{20} = -3.3^\circ$ ($c = 0.45$, 1:1 water / 95% ethanol).

Example 97

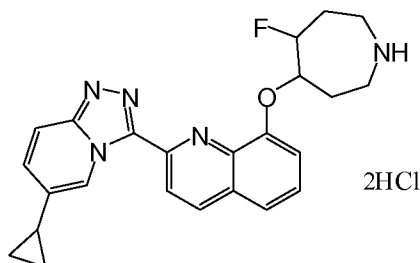


Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline dihydrochloride

[00669] Step 1: Preparation of Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline: Prepared according to the method of Example 96 using Peak 2 of non-racemic (cis)-benzyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (Example 94, Step 3D) in place of Peak 1 non-racemic (cis)-benzyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (Example 94, Step 3D) in step 1A. MS APCI (+) m/z 364.1 (M+1) detected.

[00670] Step 2: Preparation of the dihydrochloride salt of Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline: Prepared as described in Example 94 using non-racemic 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-3-fluoropiperidin-4-yloxy)quinoline in Step 4C. Specific rotation: $[\alpha]_D^{20} = +2.7^\circ$ ($c = 0.45$, 1:1 water / 95% ethanol).

Example 98



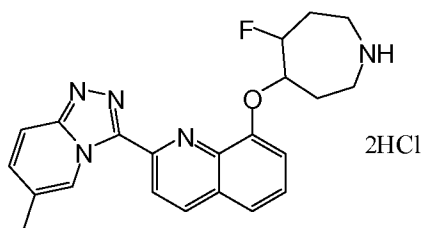
2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-5-fluoroazepan-4-yloxy)quinoline dihydrochloride

[00671] Step A: Preparation of 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol: Prepared according to the method of Example 64, Steps A-B. MS APCI (+) m/z 303 (M+1) detected.

[00672] Step B: Preparation of trans-tert-butyl 4-(2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate: Prepared according to the method of Example 90 using *cis-tert-butyl* 4-fluoro-5-(4-nitrophenylsulfonyloxy)azepane-1-carboxylate in place of *trans-tert-butyl* 4-fluoro-5-(4-nitrophenylsulfonyloxy)azepane-1-carboxylate and 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol in Step C and running the reaction at 50 °C.

[00673] Step C: Preparation of 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-5-fluoroazepan-4-yloxy)quinoline dihydrochloride: To a solution of *trans-tert-butyl* 4-(2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate (0.076 g, 0.147 mmol) in 1.5 mL DCM was added neat trifluoroacetic acid (0.339 mL, 4.40 mmol). The reaction mixture was stirred at ambient temperature for 90 minutes, then concentrated twice from DCM and dried *in vacuo*. The crude was dissolved in DCM, and a few drops of triethylamine and a few drops MeOH were added. The crude material was then purified by preparative TLC (eluting first with 9:1 DCM:6% NH₄OH in MeOH, then with 4:1 DCM:6% NH₄OH in MeOH). The product band was isolated, and the isolated material was dissolved in 1 mL DCM and a few drops of MeOH. This solution was added dropwise to a vigorously stirring solution of 1 mL 2M HCl/ether in 15 mL ether, causing a precipitate to form. The solids were isolated by filtration through a medium glass fritted funnel by pushing the solvent through with nitrogen pressure, rinsed with ether, dried under nitrogen pressure, and dried *in vacuo* to give the desired product as the dihydrochloride salt (0.036 g, 50.0 % yield) as a white powder. MS APCI (+) m/z 418 (M+1) detected.

Example 99



Enantiomer 1 of 8-((*trans*)-5-fluoroazepan-4-yloxy)-2-(6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline dihydrochloride

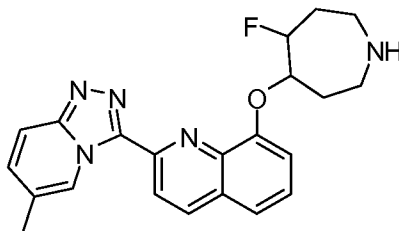
[00674] Step A: Preparation of (*trans*)-*tert*-butyl 4-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate. Prepared according to the method of Example 98, using 2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in Step A.

[00675] Step B: Preparation of enantiomer 1 of (*trans*)-*tert*-butyl 4-fluoro-5-(2-(6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)azepane-1-carboxylate. To a solution of (*trans*)-*tert*-butyl 4-(2-(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate (0.125 g, 0.225 mmol) and Pd(PPh₃)₄ (0.0519 g, 0.0449 mmol) in 1.9 mL THF was added 2M methyl zinc chloride in THF (0.225 mL, 0.449 mmol) by syringe, and the reaction mixture was heated in an 80 °C reaction block. After 6 hours, the reaction mixture was cooled to ambient temperature and saturated NH₄Cl and water were added, causing a precipitate to form. The solids were isolated by vacuum filtration through qualitative filter paper, rinsed with water, air dried, and dried *in vacuo*. The crude was purified on silica gel (1-8% MeOH in DCM gradient) to give the racemic (*trans*)-product. The resulting mixture was separated by chiral HPLC using a Chiracell OJ-H column, 9.5% EtOH in hexanes, flow rate 16 mL/min to give Peak 1 *trans*-product (0.018g, 16%, 99% ee) as a white solid, and Peak 2 *trans*-product (0.014 g, 13%, 92% ee) as a white solid.

[00676] Step C: Preparation of enantiomer 1 of 8-((*trans*)-5-fluoroazepan-4-yloxy)-2-(6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline dihydrochloride. To a solution of Peak 1 *trans*-product from Step C (0.018 g, 0.0366 mmol) in 0.8 mL DCM was added neat trifluoroacetic acid (0.141 mL, 1.83 mmol). The reaction mixture was stirred at ambient temperature for 2 hours, then concentrated to dryness and dried *in vacuo*. The resulting residue was dissolved in 1.5 mL DCM and several drops MeOH, and this solution was added to a vigorously stirring solution of 1 mL 2M HCl/ether in 10 mL ether, causing a precipitate to form. The mixture was stirred 5 minutes, then concentrated to dryness and dried *in vacuo*. The solids were dissolved in 1 mL DCM and several drops MeOH, and this solution was added dropwise to a vigorously stirring solution of 10 mL ether, causing precipitation. The solids were isolated by filtration through a 0.2 micron nylon filter membrane by pushing the solvent through with nitrogen pressure, rinsed with ether, 1:1 ether/DCM, and again with ether, dried under nitrogen pressure, and dried *in vacuo* to give the corresponding *trans*-

enantiomer 1 as the dihydrochloride salt (0.013 g, 76.5 % yield) as a pale yellow powder. MS APCI (+) m/z 392 (M+1) detected.

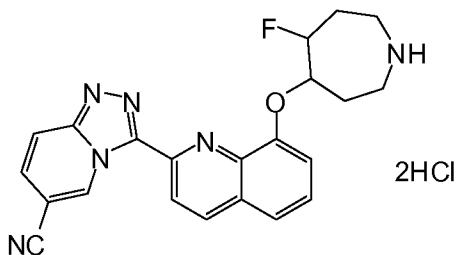
Example 100



Enantiomer 2 of 8-((*trans*)-5-fluoroazepan-4-yloxy)-2-(6-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline

[00677] Prepared according to the method of Example 99 using Peak 2 *trans*-product (from Step C) in place of Peak 1 *trans*-product in Step C. APCI (+) m/z 392 (M+1) detected.

Example 101



3-(8-((*trans*)-5-fluoroazepan-4-yloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile dihydrochloride

[00678] Step A: Preparation of 3-(8-(*tert*-butyldimethylsilyloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile. Prepared according to the method of Example 98, Steps B-C, using 5-cyano-2-hydrazinylpyridine in place of 2-hydrazinylpyridine in Step B.

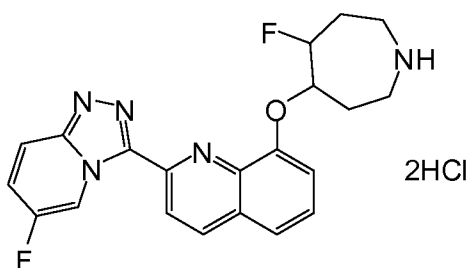
[00679] Step B: Preparation of 3-(8-hydroxyquinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile. Prepared according to the method of Example 64, using 3-(8-(*tert*-butyldimethylsilyloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile in place of 8-(*tert*-butyldimethylsilyloxy)-2-(6-cyclopropyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline in Step B and rinsing the crude product with water, ethyl acetate, and ether.

[00680] Step C: Preparation of (*trans*)-*tert*-butyl 4-(2-(6-cyano-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate. Prepared according to the method of Example 90, using *cis-tert*-butyl 4-fluoro-5-(4-nitrophenylsulfonyloxy)azepane-1-carboxylate in place of *trans-tert*-butyl 4-fluoro-5-(4-nitrophenylsulfonyloxy)azepane-1-carboxylate and 3-(8-hydroxyquinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile in

place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol in Step C and running the reaction at 50 °C.

[00681] Step D: Preparation of 3-(8-((*trans*)-5-fluoroazepan-4-yloxy)quinolin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonitrile dihydrochloride. Prepared according to the method of Example 99 using (*trans*)-*tert*-butyl 4-(2-(6-cyano-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate in place of Peak 1 *trans*-enantiomer in Step C to give the title compound as the dihydrochloride salt. MS APCI (+) *m/z* 403 (M+1) detected.

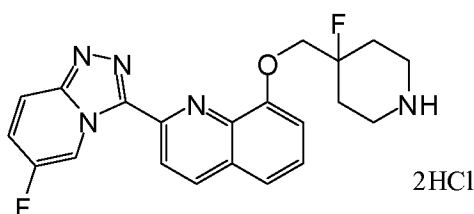
Example 102



2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((*trans*)-5-fluoroazepan-4-yloxy)quinoline dihydrochloride

[00682] Prepared according to the method of Example 101, using 5-fluoro-2-hydrazinylpyridine in place of 5-cyano-2-hydrazinylpyridine in Step A to give the title compound as the dihydrochloride salt. MS APCI (+) *m/z* 396 (M+1) detected.

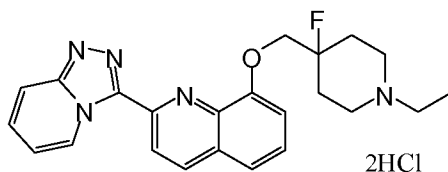
Example 103



2-(6-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline dihydrochloride

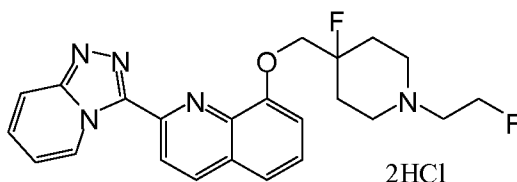
[00683] Prepared according to the method of Example 101 using 5-fluoro-2-hydrazinylpyridine in place of 5-cyano-2-hydrazinylpyridine in Step A and (4-fluoropiperidin-4-yl)methyl methanesulfonate in place of (*cis*)-*tert*-butyl 4-fluoro-5-(4-nitrophenylsulfonyloxy)azepane-1-carboxylate in Step C to give the title compound as the dihydrochloride salt. MS APCI (+) *m/z* 396 (M+1) detected.

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Example 104

2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((1-ethyl-4-fluoropiperidin-4-yl)methoxy)quinoline dihydrochloride

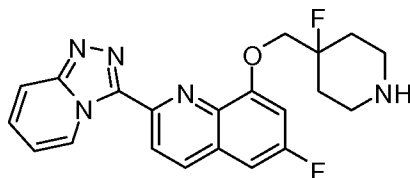
[00684] Prepared according to the method of Example 84 using acetaldehyde in place of 37% formaldehyde in water to give the title compound as the dihydrochloride salt. MS APCI (+) m/z 406 (M+1) detected.

Example 105

2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoro-1-(2-fluoroethyl)piperidin-4-yl)methoxy)quinoline dihydrochloride

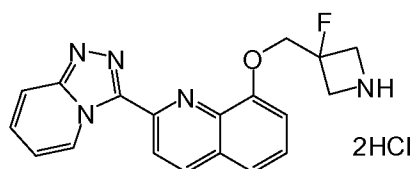
[00685] To a suspension of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((4-fluoropiperidin-4-yl)methoxy)quinoline dihydrochloride (Example 66; 0.070 g, 0.16 mmol) and 1-bromo-2-fluoroethane (0.16 g, 1.24 mmol) in 0.8 mL DMF was added DIEA (0.11 mL, 0.62 mmol). The reaction mixture was stirred at 80 °C for 5 days. The reaction mixture was concentrated, and the crude was purified twice by preparative TLC (1 mm plate, 9:1 DCM:MeOH). The resulting residue was dissolved in 0.8 mL DCM and added to a vigorously stirring solution of 1.5 mL 2M HCl/ether in 30 mL ether, causing precipitation. The mixture was concentrated and dried *in vacuo*. The resulting solids were dissolved in several drops MeOH and 1 mL DCM, and this solution was added to a vigorously stirring solution of ether, causing precipitation. The solids were isolated by filtration through a 0.2 micron nylon filter disc by pushing solvent through the filter with nitrogen pressure, rinsed with ether, 1:1 ether/DCM, and again with ether, dried under nitrogen pressure, then dried *in vacuo* to give the desired product as the dihydrochloride salt (0.020 g, 26 % yield) as an off-white powder. MS APCI (+) m/z 424 (M+1) detected.

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Example 106

2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((4-fluoropiperidin-4-yl)methoxy)quinoline dihydrochloride

[00686] Prepared according to the method of Example 66 using 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol (Example 39, Step F) in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in Step C. MS APCI (+) m/z 396 (M+1) detected.

Example 107

2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((3-fluoroazetidin-3-yl)methoxy)quinoline dihydrochloride

[00687] Step A: Preparation of *tert*-butyl 3-oxoazetidine-1-carboxylate. To a -78 °C solution of 2M oxalyl chloride (31.8 mL, 63.5 mmol) in 200 mL DCM was added DMSO (9.01 mL, 127 mmol), followed by the slow addition by addition funnel of a solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (10.0 g, 57.7 mmol) in 200 mL DCM. The cloudy reaction mixture was stirred at -78 °C for 15 minutes, then a solution triethylamine (32.2 mL, 231 mmol) in 40 mL DCM was added slowly by addition funnel. The reaction mixture was stirred another 15 minutes, the bath was removed, and the reaction was allowed to warm to ambient temperature and stirred for 15 hours. Water and brine were added, and the mixture was extracted with DCM. The combined extracts were dried (Na_2SO_4), filtered and concentrated. The crude was purified on silica gel (3-20% ethyl acetate in hexanes gradient) to give the desired product (9.0 g, 91.1 % yield) as a white solid.

[00688] Step B: Preparation of *tert*-butyl 3-methyleneazetidine-1-carboxylate. To a 0 °C mixture of KOtBu (5.90 g, 52.6 mmol) in 95 mL ether was added methyltriphenylphosphonium bromide (18.8 g, 52.6 mmol). The reaction mixture was warmed to ambient temperature and stirred 1.5 hours. A solution of *tert*-butyl 3-oxoazetidine-1-carboxylate (4.50 g, 26.3 mmol) in 10 mL ether was added. The reaction mixture was heated to reflux for 2 hours, then cooled to ambient temperature. Solids were removed by vacuum filtration through compressed Celite and rinsed with ether, and the

filtrate was concentrated. The resulting residue was suspended in 1:1 hexanes:ethyl acetate, and the solids were removed by vacuum filtration through GF/F paper and rinsed with 1:1 hexanes:ethyl acetate. The filtrate was concentrated, and the resulting oil was purified on silica gel (5-20% ethyl acetate in hexanes gradient) to give the desired product (3.50 g, 78.7 % yield) as a clear colorless oil.

[00689] Step C: Preparation of *tert*-butyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate. To a 0 °C solution of *tert*-butyl 3-methyleneazetidine-1-carboxylate (3.50 g, 20.7 mmol) in 115 mL CHCl₃ was added 77% mCPBA (13.9 g, 62.0 mmol) in 3 batches. Isopropyl alcohol (2 mL) was added. The reaction mixture was stirred for 10 minutes, then warmed to ambient temperature and stirred. After 19 hours, the milky reaction mixture was cooled to 0 °C, 10 mL isopropyl alcohol was added (reaction mixture clarified), and another 1 equivalent of mCPBA was added. The reaction mixture was warmed to ambient temperature and stirred 2 hours, then another 1 equivalent mCPBA was added portionwise. After a total of 40 hours, the reaction mixture was cooled to 0 °C, and 200 mL of 1:1 saturated Na₂S₂O₃/saturated NaHCO₃ was added slowly by pouring portionwise through ice (internal temperature was monitored; an initial 10 °C exotherm was observed). The mixture was stirred for 30 minutes, then extracted with CHCl₃, and combined extracts were dried (Na₂SO₄), filtered, and concentrated. The crude was purified on silica gel (5-50% ethyl acetate in hexanes gradient) to give the desired product (1.0 g, 26.1 % yield) as a clear colorless oil.

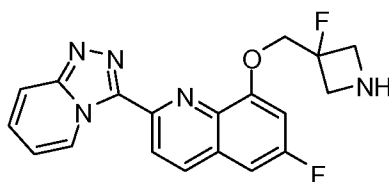
[00690] Step D: Preparation of *tert*-butyl 3-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-3-hydroxyazetidine-1-carboxylate. Prepared according to the method of Example 66 using *tert*-butyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate in place of *tert*-butyl 4-fluoro-4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate in Step C and running the reaction at 70 °C.

[00691] Step E: Preparation of *tert*-butyl 3-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-3-fluoroazetidine-1-carboxylate. (NOTE: the reaction was run in a 10 mL plastic bottle) To a 0 °C cloudy solution of *tert*-butyl 3-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-3-hydroxyazetidine-1-carboxylate (0.070 g, 0.156 mmol) in 2 mL DCM was added Deoxo-Fluor (0.0346 mL, 0.188 mmol). The reaction mixture was warmed to ambient temperature, and after 30 minutes, it was cooled back to 0 °C, and another 2 equiv. of DeoxoFluor was added, and the reaction mixture continued to stir at 0 °C. After a total of 3.5 hours, saturated NaHCO₃ was carefully added dropwise until the excess Deoxofluor was quenched. The mixture was extracted with DCM, and the combined

extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by preparative TLC (2 mm plate, 9:1 DCM:MeOH) to give the desired product (0.0156 g, 22.2 % yield) as a white foam.

[00692] Step F: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((3-fluoroazetid-3-yl)methoxy)quinoline dihydrochloride. To a solution of *tert*-butyl 3-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-3-fluoroazetid-1-carboxylate (0.016 g, 0.0356 mmol) in 1 mL DCM was added neat trifluoroacetic acid (0.137 mL, 1.78 mmol). The reaction mixture was stirred at ambient temperature for 1 hour, after which it was concentrated. The crude was purified on C18 reverse phase (10-40% acetonitrile in water gradient). The resulting solids were dissolved in 1 mL DCM plus several drops MeOH, and this solution was added to a vigorously stirring solution of 1 mL 2M HCl/ether in 15 mL ether, causing precipitation. The mixture was stirred for 5 minutes, then concentrated to dryness and dried *in vacuo*. The solids were dissolved in minimal MeOH/DCM, and this solution was added dropwise to 20 mL vigorously stirring ether, causing precipitation. The white solids were isolated by filtration through a 0.2 micron nylon filter disc by pushing solvent through with nitrogen pressure, rinsed with ether, dried under nitrogen pressure, and dried *in vacuo* to give the title compound as the dihydrochloride salt (0.002 g, 13 %) as a white powder. MS APCI (+) *m/z* 350 (M+1) detected.

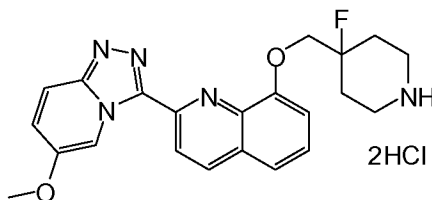
Example 108



2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((3-fluoroazetid-3-yl)methoxy)quinoline Dihydrochloride

[00693] Prepared as described for Example 107 using 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol (Example 39, Step F) in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in Step D. MS APCI (+) *m/z* 368 (M+1) detected.

Example 109



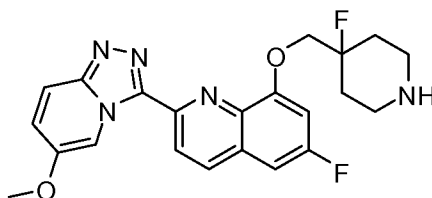
8-((4-fluoropiperidin-4-yl)methoxy)-2-(6-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline dihydrochloride

[00694] Step A: Preparation of 2-hydrazinyl-5-methoxypyridine. 2-bromo-5-methoxypyridine (4.90 g, 26.06 mmol) and anhydrous hydrazine (8.179 mL, 260.6 mmol) were combined and heated slowly to 140 °C in a sand bath and stirred for 24 hours. The reaction mixture was diluted with THF and concentrated three times. The resulting solids were suspended in 20 mL THF, stirred vigorously, and 100 mL ether was added. The resulting solids were cooled in a refrigerator for 2 hours, then isolated by filtration through a 0.4 micron nylon filter disc with nitrogen pressure, rinsed with ether, 1:1 ether:ethyl acetate, and ether, and dried *in vacuo* to give the desired product (>100 %).

[00695] Step B: Preparation of 2-(6-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol. Prepared as described for Example 1, Steps A-D, using 2-hydrazinyl-5-methoxypyridine in place of 2-hydrazinylpyridine in Step B.

[00696] Step C: Preparation of 8-((4-fluoropiperidin-4-yl)methoxy)-2-(6-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline dihydrochloride. Prepared according to the method of Example 66, Steps C-D, using 2-(6-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in place of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in Step C to give the desired product. MS APCI (+) *m/z* 408 (M+1) detected.

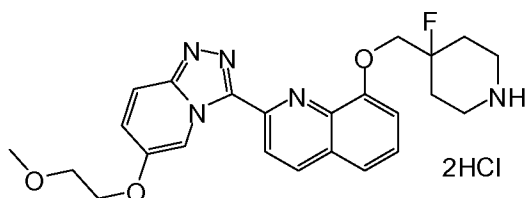
Example 110



6-fluoro-8-((4-fluoropiperidin-4-yl)methoxy)-2-(6-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline dihydrochloride

[00697] Prepared as described for Example 109 using 6-fluoro-2-(6-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (Example 39, Step F) in place of 2-(6-methoxy-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol in Step C. MS APCI (+) *m/z* 426 (M+1) detected.

Example 111

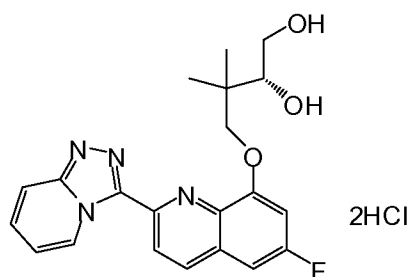


8-((4-fluoropiperidin-4-yl)methoxy)-2-(7-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline dihydrochloride

[00698] Step A: Preparation of 2-fluoro-5-(2-methoxyethoxy)pyridine. To a 0 °C suspension of Cs₂CO₃ (18.73 g, 57.48 mmol) in 150 mL DMF was added 6-fluoropyridin-3-ol (5.0 g, 44.21 mmol). The cloudy brown mixture was stirred for 15 minutes, then 1-bromo-2-methoxyethane (6.232 mL, 66.32 mmol) was added. The reaction mixture was heated in a 110 °C sand bath and stirred for 17 hours, after which it was cooled to ambient temperature and the DMF was removed *in vacuo*. The resulting residue was combined with saturated NH₄Cl and the mixture was extracted with DCM. The combined extracts were dried (Na₂SO₄), filtered, and concentrated. The crude material was purified on silica gel (5-50% ethyl acetate in hexanes gradient) to give the desired product (7.00 g, 92.50 % yield) as a clear, colorless oil.

[00699] Step B: Preparation of 8-((4-fluoropiperidin-4-yl)methoxy)-2-(7-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline dihydrochloride. Prepared as described for Example 109 using 2-fluoro-5-(2-methoxyethoxy)pyridine in place of 2-bromo-5-methoxypyridine in Step A to give the desired product as the dihydrochloride salt. MS APCI (+) *m/z* 452 (M+1) detected.

Example 112



(R)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-3,3-dimethylbutane-1,2-diol dihydrochloride

[00700] Step A: Preparation of (R)-3,3-dimethylbutane-1,2,4-triol: (R)-3-hydroxy-4,4-dimethyltetrahydrofuran-2(3H)-one (3.21 g, 24.7 mmol) was added to 30 mL THF and cooled to 0 °C. Lithium aluminum hydride (24.7 mL, 24.7 mmol) was added slowly and the reaction was warmed to ambient temperature and heated for 6 hours at reflux, during which a heterogeneous mixture of white solids formed. The reaction was cooled to ambient temperature, and 1 mL water was added, followed by the addition of 1 mL of a 15% NaOH aqueous solution (w/v) and 3 mL of water, and the reaction was stirred overnight. The reaction was passed through Celite and filtered, rinsed with copious amounts of ethyl acetate,

then dried over Na_2SO_4 . The mixture was filtered, the filtrate was concentrated, and excess water was azeotroped with toluene-DCM (1-1). The residue was dried under high vacuum for 1 hour to yield 2.4 g of the desired product as a clear thick oil.

[00701] Step B: Preparation of (R)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropan-1-ol: (R)-3,3-dimethylbutane-1,2,4-triol (2.7 g, 20 mmol) and 4-methylbenzenesulfonic acid (0.017 g, 0.10 mmol) were added to 25 mL of acetone and catalytic 4-methylbenzenesulfonic acid (0.017 g, 0.10 mmol) and stirred overnight at ambient temperature. The solution was evaporated, and to the residue was added ethyl acetate. The organic layer was washed with aqueous Na_2CO_3 , dried over MgSO_4 and filtered. The filtrate was concentrated to provide 1.7 g of the desired product as a clear oil.

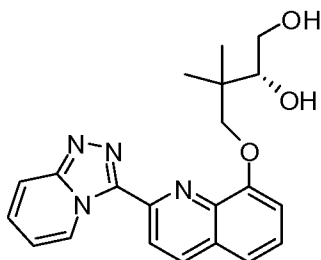
[00702] Step C: Preparation of (R)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropyl 4-nitrobenzenesulfonate: (R)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropan-1-ol (0.823 g, 4.72 mmol) was added to 10 mL of DCM and cooled to 0 °C. Triethylamine (0.982 mL, 7.09 mmol) and hypochlorous 4-nitrobenzenesulfonic anhydride (1.35 g, 5.67 mmol) were added and the solution was warmed to ambient temperature and stirred overnight. The solids were filtered off, and the filtrate was evaporated. The residue was purified on silica gel using hexane and ethyl acetate to yield 0.9 g of the desired product as a dark beige solid.

[00703] Step D: Preparation of (R)-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropoxy)-6-fluoroquinoline: 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol (0.09 g, 0.34 mmol), (R)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropyl methanesulfonate (0.11 g, 0.45 mmol) and cesium carbonate (0.22 g, 0.69 mmol) were added to 1 to 2 mL of DMA and heated to 85 °C for 4-5 hours. The reaction was concentrated and treated with water and ethyl acetate. The reaction was extracted several times with ethyl acetate. The organic layer was dried over MgSO_4 , filtered, and concentrated. The residue was purified on Silica gel using 2% NH_4OH in isopropyl acetate and DCM to provide 200 mgs of the desired product (85% pure).

[00704] Step E: Preparation of (R)-4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-3,3-dimethylbutane-1,2-diol dihydrochloride: (R)-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropoxy)-6-fluoroquinoline (0.190 g, 0.435 mmol) was added to methanol saturated with HCl and stirred for 30 minutes. The solution was evaporated, DCM was added, and the material

trituated and filtered to yield 140 mgs of the desired product as orange solid. MS ESI (+) m/z 397 (M+1) detected.

Example 113

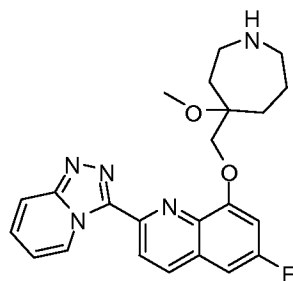


(R)-4-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3,3-dimethylbutane-1,2-diol

[00705] Step A: Preparation of (R)-2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-8-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropoxy)quinoline: 2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (0.25 g, 0.95 mmol), (R)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropyl 4-nitrobenzenesulfonate (0.41 g, 1.1 mmol) and cesium carbonate (0.62 g, 1.9 mmol) were added to minimal amount of N,N-dimethylacetamide and heated to 85 °C. The reaction was cooled, ethyl acetate was added and the mixture was sonicated. Solids were filtered off and the filtrate was dried over MgSO₄, filtered and evaporated. The crude material was purified on silica gel using isopropyl alcohol containing 2% NH₄OH and DCM to yield 30 mg of the desired product (90% pure. The crude material was used without further purification in the next step..

[00706] Step B: Preparation of (R)-4-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3,3-dimethylbutane-1,2-diol: (R)-2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-8-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropoxy)quinoline (0.030 g, 0.072 mmol) was added to 1 N HCl in methanol and stirred for 30 minutes, then evaporated, co-evaporated once in methanol and triturated in DCM to isolate 23 mg of 95% pure desired product as a beige solid. MS ESI (+) m/z 379 (M+1) detected.

Example 114



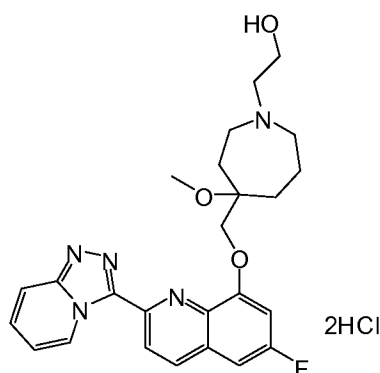
2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((4-methoxyazepan-4-yl)methoxy)quinoline bis-trifluoroacetate

[00707] Step A: Preparation of tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-hydroxyazepane-1-carboxylate: 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-ol (0.065 g, 0.25 mmol), cesium carbonate (0.16 g, 0.50 mmol) and tert-butyl 1-oxa-6-azaspiro[2.6]nonane-6-carboxylate (0.068 g, 0.30 mmol) were added to 1 mL of DMF and heated to 72 °C overnight. The reaction mixture was concentrated, and DCM was added to the residue. Solids were removed by filtration and the filtrate was purified on Silica gel using 6% NH₄OH in MeOH and DCM to yield 74 mg of the desired product as an off-white foam. MS ESI (+) *m/z* 490 (M+1) detected.

[00708] Step B: Preparation of tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)methyl)-4-methoxyazepane-1-carboxylate: tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)methyl)-4-hydroxyazepane-1-carboxylate (0.060 g, 0.106 mmol) and sodium hydride (0.00468 g, 0.117 mmol) were added to 1 mL of DMF, then iodomethane (0.00732 mL, 0.117 mmol) was added and the reaction stirred for 1 hour at ambient temperature. The reaction mixture was concentrated, and DCM was added to the residue. Solids were removed by filtration and the filtrate was purified on Silica gel using 6% NH₄OH in MeOH and DCM to yield 32 mg of the desired product as a clear oil. MS ESI (+) *m/z* 522 (M+1) detected.

[00709] Step C: Preparation of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((4-methoxyazepan-4-yl)methoxy)quinoline: tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)methyl)-4-methoxyazepane-1-carboxylate (0.032 g, 0.061 mmol) was added to a mixture of trifluoroacetic acid and DCM (1:1) for 1 hour. The reaction was concentrated and co-evaporated several times with diethyl ether to yield 32 mgs of the desired product as a white solid. MS ESI (+) *m/z* 422 (M+1) detected.

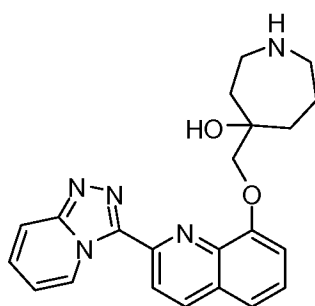
Example 115



2-((4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)methyl)-4-methoxyazepan-1-yl)ethanol) dihydrochloride

[00710] The free base of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((4-methoxyazepan-4-yl)methoxy)quinoline (prepared as described in Example 114, Step C) (0.006 g, 0.0142 mmol) was taken up in DMA and 2-bromoethanol (0.00402 mL, 0.0569 mmol) and N-isopropyl-N-methylpropan-2-amine (0.00899 mL, 0.0569 mmol) were added. The reaction mixture was stirred for 1 hour at 75 °C, then cooled, evaporated, co-evaporated with DCM. HCl in diethyl ether was added, and the resulting solids were isolated and dried to yield 6 mg of the desired product as the dihydrochloride salt. MS ESI (+) m/z 466 (M+1) detected.

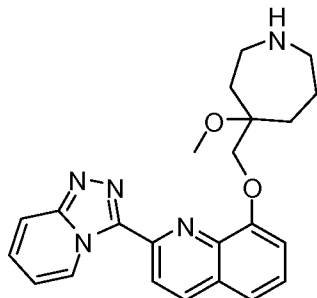
Example 116



4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)azepan-4-ol bis-trifluoroacetate

[00711] Step A: Preparation of tert-butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-hydroxyazepane-1-carboxylate: 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (0.09 g, 0.34 mmol), tert-butyl 1-oxa-6-azaspiro[2.6]nonane-6-carboxylate (0.086 g, 0.38 mmol) and cesium carbonate (0.22 g, 0.69 mmol) were added to 1 mL of DMA in a sealed vial and heated to 70 °C overnight. The reaction was concentrated, and the residue was purified on Silica gel using 6 % NH₄OH in MeOH and CHCl₃ to yield 56 mgs of 70 % pure desired product (contaminated with starting phenol). MS ESI (+) m/z 490 (M+1) detected.

[00712] Step B: Preparation of 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)azepan-4-ol: tert-Butyl 4-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-hydroxyazepane-1-carboxylate (0.0039 g, 0.0080 mmol) was treated with a mixture of trifluoroacetic acid and DCM (1:1) for 1 hour. The reaction was concentrated to provide 4 mgs of the desired material as a solid. MS ESI (+) m/z 390 (M+1) detected.

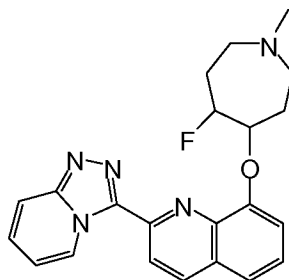
Example 117

2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-8-((4-methoxyazepan-4-yl)methoxy)quinoline
dihydrochloride

[00713] Step A: Preparation of tert-butyl 4-((2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-hydroxyazepane-1-carboxylate: Prepared according to the procedure described in Example 116, Step A.

[00714] Step B: Preparation of tert-butyl 4-((2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-methoxyazepane-1-carboxylate: tert-Butyl 4-((2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-hydroxyazepane-1-carboxylate (0.056 g, 0.114 mmol), iodomethane (0.00858 mL, 0.137 mmol) and sodium hydride (0.00915 g, 0.229 mmol) were added to DMF (1 mL) at ambient temperature and stirred for 2 hours. The reaction was concentrated and the residue was purified on Silica gel using methanol (containing 6% NH₄OH) and DCM, to yield 39 mg of the desired product (67 % pure). MS ESI (+) *m/z* 504 (M+1) detected.

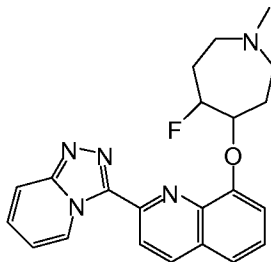
[00715] Step C: Preparation of 2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-8-((4-methoxyazepan-4-yl)methoxy)quinoline: tert-Butyl 4-((2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-4-methoxyazepane-1-carboxylate (0.040 g, 0.079 mmol) was added to a mixture of trifluoroacetic acid and DCM (1:1) for 30 minutes, and the reaction was concentrated. Ethyl acetate was added and the suspension was filtered through a Waters filter (to remove any errant silica gel), and the filtrate was concentrated. DCM was added followed by precipitation with HCl dissolved in diethyl ether, evaporated, co-evaporated in diethyl ether to yield 16 mgs of the desired product as a yellow solid (95% pure by LC). MS ESI (+) *m/z* 404 (M+1) detected.

Example 118

Stereoisomers 1 and 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-5-fluoro-1-methylazepan-4-yloxy)quinoline

[00716] Step A: Preparation of Stereoisomers 1 and 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((5-fluoroazepan-4-yloxy)quinoline: A mixture of *cis* and *trans tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate was prepared according to Example 46, Step E. The crude material was purified by column chromatography (Biotage SP1, 340G SNAP, 15% to 60% EtOAc/hexanes), and the first eluting material was collected to provide a racemic mixture of the Stereoisomers 1 and 2 as a thick colorless oil which slowly became a white solid.

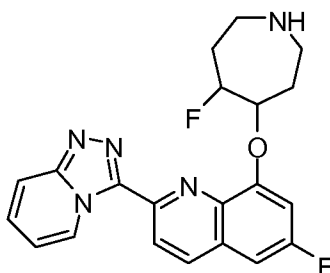
[00717] Step B: Preparation of Stereoisomers 1 and 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-5-fluoro-1-methylazepan-4-yloxy)quinoline: A mixture of Stereoisomers 1 and 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((trans)-5-fluoroazepan-4-yloxy)quinoline (0.023 g, 0.0511 mmol) was slurried in CH₂Cl₂ (3 mL). A saturated aqueous Na₂CO₃ solution (5 mL) was added and the mixture was stirred at ambient temperature for 0.5 hours. The layers were separated and the aqueous phase was extracted with CH₂Cl₂. The combined organic layers were washed with brine and dried over Na₂SO₄, filtered and concentrated. The crude residue was treated with formic acid (0.289 mL, 7.66 mmol) and formaldehyde (0.0380 mL, 0.511 mmol). The mixture was stirred at 90 °C for 4 hours. The mixture was cooled to ambient temperature and carefully treated with a saturated aqueous Na₂CO₃ solution to adjust the mixture to about pH 11. The mixture was extracted with CHCl₃ and the combined organic phases were washed with brine and dried over Na₂SO₄, filtered and concentrated. The crude product was purified by Preparative TLC (0.5 mm, 10% MeOH/CH₂Cl₂ with 1% 7N NH₃/MeOH) to provide the desired product (0.011 g, 55%) as a white solid. MS ESI (+) *m/z* 392.1 (M+1) detected.

Example 119

Stereoisomers 3 and 4 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoro-1-methylazepan-4-yloxy)quinoline

[00718] Step A: Preparation of Stereoisomers 3 and 4 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-((5-fluoroazepan-4-yloxy)quinoline: A mixture of *cis* and *trans* *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate was prepared according to Example 46, Step E. The crude material was purified by column chromatography (Biotage SP1, 340G SNAP, 15% to 60% EtOAc/hexanes), and the second eluting material was collected to provide a racemic mixture of the Stereoisomers 3 and 4 of isomers as a thick colorless oil which slowly became a white solid.

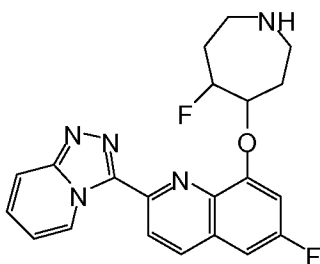
[00719] Step B: Preparation of Stereoisomers 3 and 4 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(5-fluoro-1-methylazepan-4-yloxy)quinoline: A mixture of Stereoisomers 3 and 4 of *tert*-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-5-fluoroazepane-1-carboxylate (0.021 g, 0.0440 mmol) was dissolved in formic acid (0.332 mL, 8.80 mmol). Formaldehyde (0.0327 mL, 0.440 mmol, 37% aqueous) was added, and the mixture was stirred at 90 °C for 4 hours. The mixture was cooled to ambient temperature and treated with a saturated aqueous Na₂CO₃ solution to adjust the mixture to about pH 11. The mixture was extracted with CHCl₃ and the combined organic phases were washed with brine and dried over Na₂SO₄, filtered and concentrated. The crude product was purified by Preparative TLC (0.5 mm, 10% MeOH/CH₂Cl₂ with 1% 7N NH₃/MeOH) to provide the desired product (0.016g, 93%) as a white solid. MS ESI (+) *m/z* 392.1 (M+1) detected.

Example 120

Enantiomer 2 of 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((cis)-5-fluoroazepan-4-yloxy)quinoline

[00720] Enantiomer 2 of (cis)-tert-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-5-fluoroazepane-1-carboxylate (Example 90, Step D; 0.119 g, 0.240 mmol) was dissolved in CHCl_3 (2.4 mL). HCl (2.40 mL, 9.61 mmol, 4.0M Dioxane) was added and the mixture was stirred at ambient temperature for 3 hours. The mixture was filtered through a polypropylene filter and washed with CH_2Cl_2 and then Et_2O , then slurried in hexanes and dried carefully *in vacuo* to provide 0.095 g of the desired product as a white solid (85%). MS ESI (+) m/z 396.1 (M+1) detected.

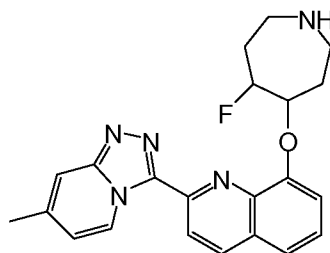
Example 121



2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoro-8-((trans)-5-fluoroazepan-4-yloxy)quinoline

[00721] Enantiomer 1 of *trans*-tert-butyl 4-(2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-6-fluoroquinolin-8-yloxy)-5-fluoroazepane-1-carboxylate (Peak 1 from Example 91, Step E; 0.210 g, 0.424 mmol) was dissolved in CHCl_3 (4.3 mL). To this solution was added HCl (4.24 mL, 17.0 mmol, 4.0M Dioxane) and the mixture was stirred at ambient temperature for 3 hours. The mixture was filtered through a polypropylene filter and washed with CH_2Cl_2 and Et_2O , slurried in hexanes and then dried carefully *in vacuo* to provide the desired product as white solid. MS ESI (+) m/z 396.1 (M+1) detected.

Example 122

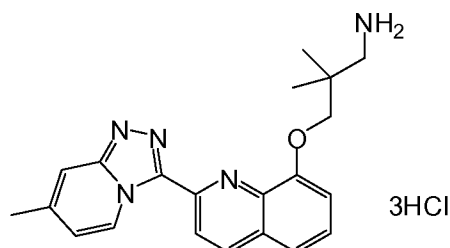


8-((cis)-4,5)-5-fluoroazepan-4-yloxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline

[00722] Enantiomer 2 of *cis*-tert-butyl 4-fluoro-5-(2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)azepane-1-carboxylate (Peak 2 from Example 92, Step F; 0.161 g, 0.328 mmol) was dissolved in CHCl_3 (3 mL). To this solution was added HCl (6.55

mL, 13.1 mmol, 2.0M Et₂O) and the mixture was stirred at ambient temperature for 4 hours. The mixture was then filtered through a polypropylene filter and washed with CH₂Cl₂ and then Et₂O and finally slurried in hexanes then dried carefully *in vacuo* to provide the desired product as a white solid. MS ESI (+) *m/z* 392.1 (M+1) detected.

Example 123



2,2-dimethyl-3-(2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propan-1-amine trihydrochloride

[00723] Step A: Preparation of (E/Z)-8-(tert-butyldimethylsilyloxy)-2-((2-(4-methylpyridin-2-yl)hydrazono)methyl)quinoline: A mixture of 8-(tert-butyldimethylsilyloxy)quinoline-2-carbaldehyde (6.11 g, 21.3 mmol) and 2-hydrazinyl-4-methylpyridine (2.62 g, 21.3 mmol) in ethanol (60 mL) was stirred at ambient temperature overnight. The resulting precipitate was filtered, washed with cold ethanol and dried *in vacuo* to provide 5.92 g (71%) of desired product as a beige-colored solid.

[00724] Step B: Preparation of 8-(tert-butyldimethylsilyloxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline: To a suspension of (E/Z)-8-(tert-butyldimethylsilyloxy)-2-((2-(4-methylpyridin-2-yl)hydrazono)methyl)quinoline (5.92 g, 15.1 mmol) in dichloromethane (50 mL) was added iodosobenzene diacetate (5.34 g, 16.6 mmol). The mixture was stirred at ambient temperature overnight and then concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 1:4 ethyl acetate/hexanes followed by 1:2 ethyl acetate/hexanes to provide 5.00 g (85%) of desired product.

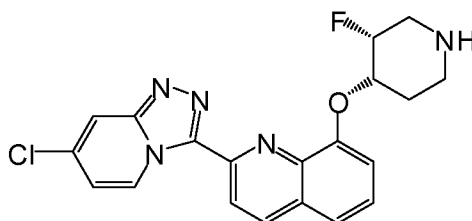
[00725] Step C: Preparation of 2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol: To a solution of 8-(tert-butyldimethylsilyloxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline (5.00 g, 12.8 mmol) in tetrahydrofuran (100 mL) at 0 °C was added tetrabutylammonium fluoride (19.2 mL, 1 M in tetrahydrofuran, 19.2 mmol). The reaction was stirred for 6 hours at ambient temperature and then diluted with saturated aqueous ammonium chloride. The mixture was concentrated under reduced

pressure, triturated with water, filtered and air-dried to provide 3.50 g (99%) of desired product as a white solid.

[00726] Step D: Preparation of tert-butyl 2,2-dimethyl-3-(2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propylcarbamate: A mixture of 2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (prepared according to Example 1; 50 mg, 0.18 mmol), 3-(tert-butoxycarbonylamino)-2,2-dimethylpropyl methanesulfonate (102 mg, 0.36 mmol) and cesium carbonate (118 mg, 0.36 mmol) in dimethylacetamide (2 mL) was heated to 50 °C overnight. The mixture was concentrated under reduced pressure and purified by successive silica gel chromatography, eluting with 1:9 methanol/dichloromethane and a gradient of dichloromethane to 1:9 methanol/dichloromethane. The residue was then purified by preparative thin layer chromatography eluting with 3:7 acetone/dichloromethane to provide 35 mg (42%) of desired product as a light yellow solid.

[00727] Step E: Preparation of 2,2-dimethyl-3-(2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propan-1-amine trihydrochloride: A mixture of tert-butyl 2,2-dimethyl-3-(2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)propylcarbamate (35 mg, 0.076 mmol) and hydrochloric acid (4 M in dioxane, 0.57 mL, 2.3 mmol) in dichloromethane (0.5 mL) was stirred overnight. The reaction was concentrated under reduced pressure. The residue was evaporated from twice from toluene, once from hexanes, triturated with hexanes, filtered and dried *in vacuo* to provide 25 mg (70%) of desired product as the trihydrochloride salt. MS ESI (+) *m/z* 362 (M+1) detected.

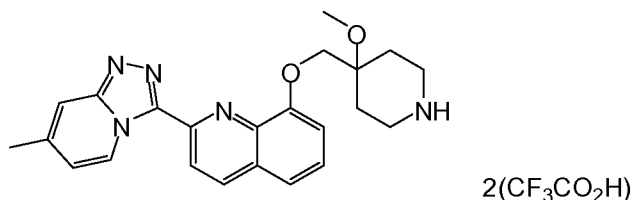
Example 124



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

[00728] Prepared according to the method of Example 123 using 4-chloro-2-hydrazinylpyridine in place of 2-hydrazinyl-4-methylpyridine in Step A and (3R,4R)-tert-butyl-3-fluoro-4-(methylsulfonyloxy)piperidine-1-carboxylate in place of 3-(tert-butoxycarbonylamino)-2,2-dimethylpropyl methanesulfonate in Step D. MS ESI (+) *m/z* 398 (M+1) detected.

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Example 125

8-((4-methoxypiperidin-4-yl)methoxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline di-trifluoroacetate

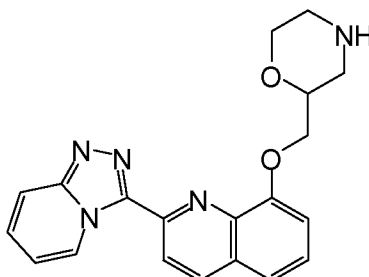
[00729] Step A: Preparation of tert-butyl 4-hydroxy-4-((2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)piperidine-1-carboxylate: A mixture of 2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-ol (prepared according to Example 1; 20 mg, 0.72 mmol), tert-butyl-1-oxa-6-azaspiro[2.5]octane-6-carboxylate (178 mg, 0.83 mmol) and cesium carbonate (472 mg, 1.5 mmol) in dimethylacetamide (2.5 mL) was heated to 98 °C overnight. The mixture cooled to ambient temperature, filtered through celite and concentrated under reduced pressure. The residue was purified by silica gel chromatography with a gradient of dichloromethane to 1:9 methanol/dichloromethane to provide 170 mg (48%) of desired product.

[00730] Step B: Preparation of tert-butyl 4-methoxy-4-((2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)piperidine-1-carboxylate: A mixture of tert-butyl 4-hydroxy-4-((2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)piperidine-1-carboxylate (50 mg, 0.10 mmol) and sodium hydride (18 mg, 0.82 mmol) in dimethylformamide (1 mL) was stirred at ambient temperature for 15 minutes. Iodomethane (0.051 mL, 0.82 mmol) was added and the solution was stirred at ambient temperature overnight. The reaction was concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed twice with saturated aqueous ammonium carbonate. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated with hexanes and further purified by preparative thin layer chromatography with 1:9 methanol/dichloromethane to provide 25 mg (46%) of desired product.

[00731] Step C: Preparation of 8-((4-methoxypiperidin-4-yl)methoxy)-2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinoline di-trifluoroacetate: A mixture of tert-butyl 4-methoxy-4-((2-(7-methyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)piperidine-1-carboxylate (30 mg, 0.060 mmol) and trifluoroacetic acid (0.37 mL, 4.8 mmol) in dichloromethane (1 mL) was at ambient temperature for 30 minutes. The

reaction was concentrated under reduced pressure. The residue was triturated with diethyl ether, filtered and dried *in vacuo* to provide 12 mg (52%) of desired product as the di-trifluoroacetate salt. MS ESI (+) m/z 404 (M+1) detected.

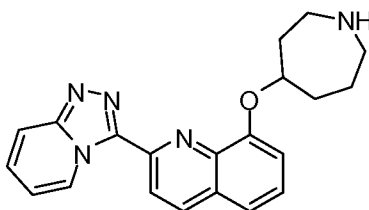
Example 126



2-((2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)morpholine

[00732] Prepared according to the method of Example 16 using tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate in place of tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate. MS ESI (+) m/z 362.1 (M+1) detected.

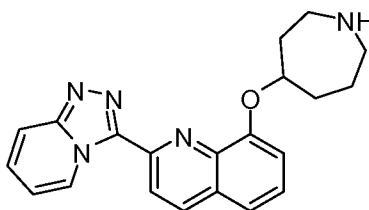
Example 127



Enantiomer 1 of 2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline

[00733] Prepared according to the procedure of Example 90, using 2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline (Example 52) as the starting material. Racemic-2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline-1-carboxylate was separated by chiral HPLC on a Prep Chiral OJ-H column using the following solvent mixture: 75% heptane, 20% EtOH, 3% MeOH, 2% acetonitrile, to provide the enantiomers as peak 1 (7.32 minutes) and peak 2 (8.54 minutes). Peak 1 was isolated to provide the title compound 99% ee. MS ESI (+) m/z 360.1 (M+1) detected.

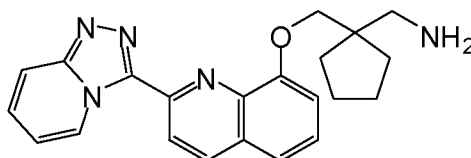
Example 128



Enantiomer 2 of 2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline

[00734] Prepared according to the procedure of Example 90, using 2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline (Example 52) as the starting material. Racemic-2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-8-(azepan-4-yloxy)quinoline-1-carboxylate was separated by chiral HPLC on a Prep Chiral OJ-H column using the following solvent mixture: 75% heptane, 20% EtOH, 3% MeOH, 2% acetonitrile, to provide the enantiomers as peak 1 (7.32 minutes) and peak 2 (8.54 minutes). Peak 2 was isolated to provide the title compound 98% ee. MS ESI (+) m/z 360.1 (M+1) detected.

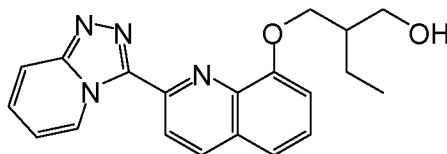
Example 129



(1-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)cyclopentyl)methanamine

[00735] Prepared according to the method of Example 16 using tert-butyl (1-(hydroxymethyl)cyclopentyl)methylcarbamate in place of tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate. MS ESI (+) m/z 374.5 (M+1) detected.

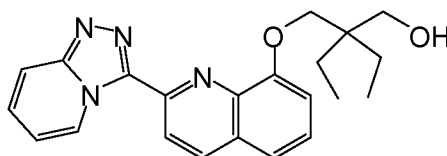
Example 130



2-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)butan-1-ol

[00736] Prepared according to the method of Example 22, using 2-ethylpropane-1,3-diol in place of 1,1-bis(hydroxymethyl)cyclopropane. MS ESI (-) m/z 347.2 (M-1) detected.

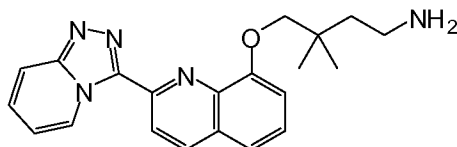
Example 131



2-((2-([1,2,4]triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)methyl)-2-ethylbutan-1-ol

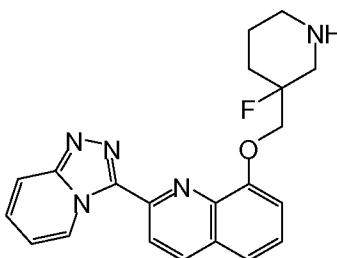
[00737] Prepared according to the method of Example 22, using 2,2-diethylpropane-1,3-diol in place of 1,1-bis(hydroxymethyl)cyclopropane. MS ESI (-) m/z 377.2 (M+1) detected.

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Example 132

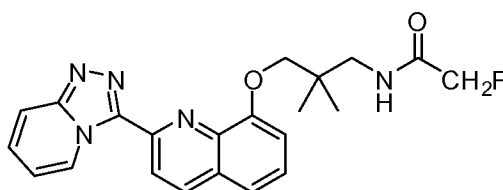
4-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-3,3-dimethylbutan-1-amine

[00738] Prepared according to the method of Example 18, using tert-butyl 4-hydroxy-3,3-dimethylbutylcarbamate in place of tert-butyl 3-hydroxy-2,2-dimethylpropylcarbamate. MS ESI (+) m/z 362.3 (M+1) detected.

Example 133

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

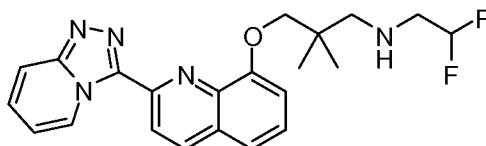
[00739] Prepared according to the method of Example 16, using tert-butyl 3-fluoro-3-(hydroxymethyl)piperidine-1-carboxylate in place of using tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate. MS ESI (+) m/z 378.2 (M+1) detected.

Example 134

N-(3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropyl)-2-fluoroacetamide

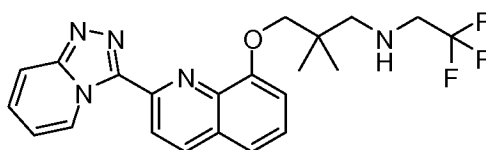
[00740] 2-Fluoroacetyl chloride (12 mg, 0.13 mmol) was added to a stirred solution of 3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine (prepared according to Example 18; 30 mg, 0.086 mmol) and diisopropylethyl amine (45 μ L, 0.26 mmol) in DCM (2 mL) at 0 °C. After 30 minutes, the reaction was quenched with saturated aqueous bicarbonate (5 mL), extracted into EtOAc, washed with water, dried over Na₂SO₄ followed by concentration in vacuo. The resulting oil was purified by flash column chromatography (silica gel), eluting with 100% EtOAc (Biotage) to give the desired product (12 mg, 0.029 mmol, 34 % yield) as a white solid. MS ESI (+) m/z 408.2 (M+1) detected.

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Example 135

3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-N-(2,2-difluoroethyl)-2,2-dimethylpropan-1-amine hydrochloride

[00741] 2,2-diFluoroethyl trifluoromethanesulfonate (17 μ L, 0.13 mmol) was added to a stirred solution of 3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethylpropan-1-amine (30 g, 0.086 mmol) and diisopropylethyl amine (39 μ L 0.22 mmol) in dry THF/DMF (1mL/1mL) at ambient temperature. After stirring overnight, the reaction was diluted with EtOAc, washed with saturated aqueous bicarbonate, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel), eluting with 50% EtOAc/hexanes, affording the desired product (10 mg). MS ESI (+) m/z 412.2 (M+1) detected.

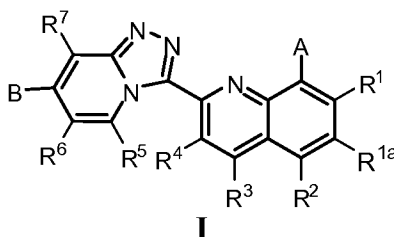
Example 136

3-(2-((1,2,4)triazolo[4,3-a]pyridin-3-yl)quinolin-8-yloxy)-2,2-dimethyl-N-(2,2,2-trifluoroethyl)propan-1-amine

[00742] Prepared according to the method of Example 135, using 2,2,2-trifluoroethyl trifluoromethanesulfonate in place of 2,2-difluoroethyl trifluoromethanesulfonate. MS ESI (+) m/z 430.2 (M+1) detected.

What is claimed is:

1. A compound of general Formula I:



- 5 or a pharmaceutically acceptable salt thereof, wherein:

A is OR¹⁰ or NR¹¹R¹²;

B is H, F, Cl, OR^a, (1-6C alkyl)NR^bR^c, (1-6C alkyl)OH, CH(OH)CH₂OH, or (1-4C alkyl);

R¹ is H, F, Cl, Br, Me, cyclopropyl or CN;

10 R^{1a}, R², R³ and R⁴ are independently H, F, Cl, Br, Me or CN;

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

R⁶ is H, F, Me, Br, CN, cyclopropyl, phenyl, MeO- or MeOCH₂CH₂O-;

15 R¹⁰ is H, hetCyc¹, -(1-3C alkyl)hetCyc^{1a}, hetCyc², (CR¹⁷R¹⁸)_p(CR¹³R¹⁴)CH₂NR¹⁵R¹⁶, -(CR¹⁷R¹⁸)_p(CR¹³R¹⁴)CH₂OH, (1-6C alkyl), hetAr¹, (1-3C alkyl)hetAr^{1a}, or (3-7C)cycloalkyl substituted with NH₂, NH(1-6C alkyl) or N(1-6C alkyl)₂;

R¹¹ is H or (1-6C)alkyl;

20 R¹² is hetCyc³, (1-6C alkyl)NR¹⁵R¹⁶, C(O)(1-6C alkyl)NR¹⁵R¹⁶, (1-6C alkyl)NHC(O)O(1-6C alkyl), or (4-7C)cycloalkyl optionally substituted with OH, NH₂, NH(1-6C alkyl) or N(1-6C alkyl)₂;

R¹³ is H, (1-6C)alkyl, F or OH, and

R¹⁴ is H, (1-6C)alkyl or F, or

R¹³ and R¹⁴ together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

25 each R¹⁵, R¹⁶, R¹⁷ and R¹⁸ is independently H or (1-6C)alkyl,

or each R¹⁵, R¹⁷ and R¹⁸ is independently H or (1-6C)alkyl and R¹⁶ is H, (1-6C)alkyl, C(=O)CH₂F, CH₂CHF₂ or CH₂CF₃;

or NR¹⁵R¹⁶ forms a 5-6 membered heterocyclic ring having a first ring heteroatom which is N and optionally having a second ring heteroatom selected from N and O;

hetCyc¹, hetCyc^{1a}, and hetCyc³ are independently a 4-7 membered heterocycle having a ring nitrogen atom and optionally substituted with one or more R⁹ groups, or

hetCyc¹ and hetCyc³ are independently a 4-7 membered heterocycle having a ring nitrogen atom and optionally substituted with one or more R⁹ groups, and hetCyc^{1a} is
 5 selected from a morpholinyl and 4-7 membered azacyclic ring optionally substituted with one or more R⁹ groups;

each R⁹ is independently selected from halogen, (1-6C)alkyl, cyclopropylmethyl, benzyl, NR^fR^g, -(1-6C alkyl)NR^hRⁱ, OR^j, (1-6C alkyl)OR^k, (1-6C)fluoroalkyl, C(O)NR^mRⁿ, (1-6C alkyl)C(O)NR^pR^q, and C(O)O(1-6C alkyl);

10 hetCyc² is an 8-membered bridged heterocycle having a ring nitrogen atom;

hetAr¹ and hetAr^{1a} are independently a 5 or 6 membered heteroaryl having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from F, Cl, Br, Me, cyclopropyl, CN, NH₂, NH(1-6C alkyl) and N(1-6C alkyl)₂;

15 R^a is H, (1-6C alkyl), -(1-6C alkyl)-O-(1-6C alkyl) or -(1-6C alkyl)-O-(3-6C cycloalkyl);

each R^b, R^f, R^g, R^h, Rⁱ, R^k, R^m, R^p and R^q is independently selected from H and (1-6C alkyl);

R^j is H, (1-6C alkyl) or cyclopropyl;

20 Rⁿ is H, (1-6C alkyl), -O(1-6C alkyl) or -O(3-6C cycloalkyl); and
 p is 0, 1 or 2.

2. A compound of claim 1, wherein:

A is OR¹⁰ or NR¹¹R¹²;

25 B is H, F, OR^a, (1-6C alkyl)NR^bR^c, (1-6C alkyl)OH, CH(OH)CH₂OH or (1-4C alkyl);

R¹ is H, F, Cl, Br, Me, cyclopropyl or CN;

R^{1a}, R², R³ and R⁴ are independently H, F, Cl, Br, Me or CN;

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

R⁶ is H, F, Me, Br, CN, cyclopropyl or phenyl;

30 R¹⁰ is H, hetCyc¹, -(1-3C alkyl)hetCyc^{1a}, hetCyc², -(CR¹⁷R¹⁸)_p(CR¹³R¹⁴)CH₂NR¹⁵R¹⁶, -(CR¹⁷R¹⁸)_p(CR¹³R¹⁴)CH₂OH, (1-6C alkyl), hetAr¹, (1-3C alkyl)hetAr^{1a}, or (3-7C)cycloalkyl substituted with NH₂, NH(1-6C alkyl) or N(1-6C alkyl)₂;

R¹¹ is H or (1-6C)alkyl;

R^{12} is hetCyc³, (1-6C alkyl)NR¹⁵R¹⁶, C(O)(1-6C alkyl)NR¹⁵R¹⁶, (1-6C alkyl)NHC(O)O(1-6C alkyl), or (4-7C)cycloalkyl optionally substituted with OH, NH₂, NH(1-6C alkyl) or N(1-6C alkyl)₂;

R^{13} is H, (1-6C)alkyl, F or OH, and

5 R^{14} is H, (1-6C)alkyl or F, or

R^{13} and R^{14} together with the carbon atom to which they are attached form a 3-6 membered carbocyclic ring;

each R^{15} , R^{16} , R^{17} and R^{18} is independently H or (1-6C)alkyl,

10 or NR¹⁵R¹⁶ forms a 5-6 membered heterocyclic ring having a first ring heteroatom which is N and optionally having a second ring heteroatom selected from N and O;

hetCyc¹, hetCyc^{1a}, and hetCyc³ are independently a 4-7 membered heterocycle having a ring nitrogen atom and optionally substituted with one or more R^9 groups;

15 each R^9 is independently selected from halogen, (1-6C)alkyl, cyclopropylmethyl, benzyl, NR^fR^g, -(1-6C alkyl)NR^hRⁱ, OR^j, (1-6C alkyl)OR^k, (1-6C)fluoroalkyl, C(O)NR^mRⁿ, (1-6C alkyl)C(O)NR^pR^q, and C(O)O(1-6C alkyl);

hetCyc² is an 8-membered bridged heterocycle having a ring nitrogen atom;

20 hetAr¹ and hetAr^{1a} are independently a 5 or 6 membered heteroaryl having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from F, Cl, Br, Me, cyclopropyl, CN, NH₂, NH(1-6C alkyl) and N(1-6C alkyl)₂;

R^a is H, (1-6C alkyl), -(1-6C alkyl)-O-(1-6C alkyl) or -(1-6C alkyl)-O-(3-6C cycloalkyl);

each R^b , R^f , R^g , R^h , R^i , R^k , R^m , R^p and R^q is independently selected from H and (1-6C alkyl);

25 R^j is H, (1-6C alkyl) or cyclopropyl;

R^n is H, (1-6C alkyl), -O(1-6C alkyl) or -O(3-6C cycloalkyl); and

p is 0, 1 or 2.

3. The compound of claim 1 or 2, where B is H, F, OR^a, (1-6C alkyl)NR^bR^c, (1-6C alkyl)OH, or CH(OH)CH₂OH.

30 4. The compound according to any of claims 1-3, wherein A is OR¹⁰.

5. The compound of claim 4, wherein R^{10} is hetCyc¹, -(1-3Calkyl)hetCyc^{1a} or hetCyc², wherein hetCyc¹ and hetCyc^{1a} are optionally substituted with one or more R^9 groups.

6. The compound of claim 5, wherein each R⁹ is independently selected from F, (1-6C)alkyl, C(O)O(1-6C)alkyl, (1-6C alkyl)OR^k, C(O)NR^mRⁿ, (1-6C alkyl)C(O)NR^pR^q, and OR^j.

7. The compound of claim 6, wherein hetCyc¹ and -(1-3C alkyl)hetCyc^{1a} are optionally substituted with one or two R⁹ groups independently selected from Me, Et, isopropyl, cyclopropylmethyl, F, OH, OMe, CH₂OH, CH₂CH₂OH, CH₂CH₂F, CH₂OMe, C(=O)OMe, C(=O)NH₂ and CH₂C(=O)NH₂.

8. The compound of claim 4, wherein R¹⁰ is -(CR¹⁷R¹⁸)_p(CR¹³R¹⁴)CH₂NR¹⁵R¹⁶.

9. The compound of claim 4, wherein R¹⁰ is -(CR¹⁷R¹⁸)_p(CR¹³R¹⁴)CH₂OH.

10. The compound of claim 4, wherein R¹⁰ is (1-6C alkyl).

11. The compound of claim 4, wherein R¹⁰ is (3-7C)cycloalkyl substituted with NH₂, NH(1-6C alkyl) or N(1-6C alkyl)₂.

12. The compound of claim 4, wherein R¹⁰ is hetAr¹ or (1-3C alkyl)hetAr^{1a}.

13. The compound according to any of claims 1-3, wherein A is NR¹¹R¹².

14. The compound of claim 13, wherein R¹² is hetCyc³ optionally substituted with one or more R⁹ groups.

15. The compound of claim 14, wherein each R⁹ is independently selected from (1-6C) alkyl.

16. The compound of claim 13, wherein R¹² is (4-7C)cycloalkyl optionally substituted with OH, NH₂, NH(1-6C alkyl) or N(1-6C alkyl)₂.

17. The compound of claim 13, wherein R¹² is (1-6C alkyl)NR¹⁵R¹⁶, C(O)(1-6C alkyl)NR¹⁵R¹⁶ or (1-6 C alkyl)NHC(O)(1-6C alkyl).

18. The compound as defined in any of claims 1-17, wherein B is H.

19. The compound as defined in any of claims 1-17, wherein B is OR^a.

20. The compound of claim 19, wherein B is selected from OMe, -OCH₂CH₂OMe and -OCH₂CH₂O(cyclopropyl).

21. The compound as defined in any of claims 1-17 wherein B is F.

22. The compound as defined in any of claims 1-17, wherein B is (1-6C alkyl)NR^bR^c.

23. The compound as defined in any of claims 1-17, wherein B is (1-6C alkyl)OH.

24. The compound as defined in any of claims 1-17, wherein B is CH(OH)CH₂OH.

25. The compound as defined in any of claims 1-17, wherein B is (1-4C alkyl).

26. The compound of claim 1, wherein B is Cl.

5 27. The compound as defined in any of claims 1-26, wherein each of R¹, R², R³, R⁵ and R⁷ is hydrogen.

28. A pharmaceutical composition, which comprises a compound of Formula I as defined in any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

10 29. A compound of Formula I as defined in any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory or autoimmune disease.

30. A compound as defined in claim 29, wherein the inflammatory or autoimmune disease is multiple sclerosis, lupus or inflammatory bowel disease.

15 31. A compound of Formula I as defined in any one of claims 1 to 27 or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

32. A method of treating a PIM-1 and/or PIM-2 and/or PIM-3 kinase-mediated condition in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I as defined in any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof.

20 33. A method of treating an inflammatory or autoimmune disorder in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I as defined in any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof.

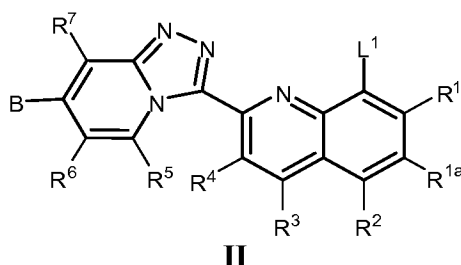
25 34. The method as defined in claim 33 wherein the inflammatory or autoimmune disease is multiple sclerosis, lupus or inflammatory bowel disease.

35. A method of treating cancer in a patient in need thereof, comprising administering to said patient a compound as defined in any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof.

30 36. A process for the preparation a compound of claim 1, which comprises:

(a) for a compound of Formula I wherein A is NR¹¹R¹², coupling a corresponding compound having the formula II

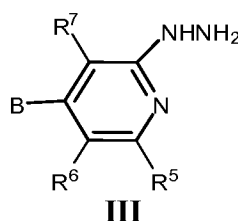
152



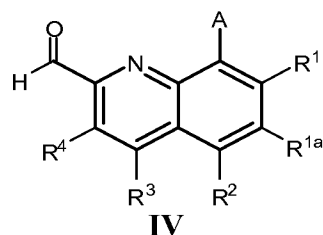
wherein L^1 represents a leaving atom or group, with a compound having the formula $HNR^{11}R^{12}$, using a palladium (II) catalyst and a ligand in the presence of a base;

5 or

(b) reacting a compound of Formula **III**



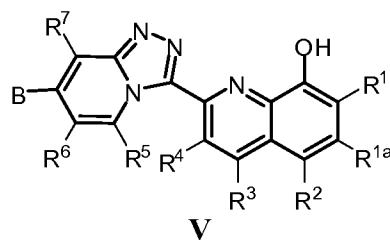
with a compound having the Formula **IV**



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in the presence of an organo hypervalent iodine reagent; or

(c) for a compound of Formula **I** wherein A is OR^{10} , coupling a corresponding compound having the Formula **V**



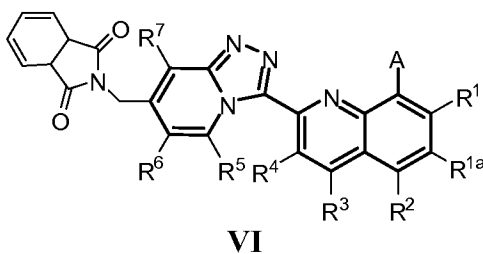
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with a compound having the formula $HO-R^{10}$ in the presence of a coupling agent and triphenylphosphine in a suitable solvent; or

(d) for a compound of Formula **I** wherein B is $(CH_2)NR^bR^c$, reacting a corresponding compound having the Formula **VI**

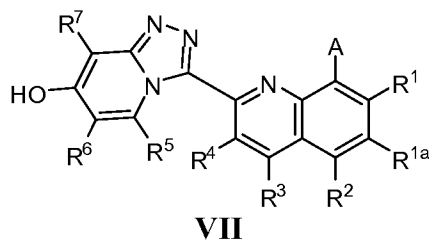
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with hydrazine; or

- (e) for a compound of Formula I where B is OR^a, reacting a corresponding
 5 compound having the Formula VII



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

- 10 removing any protecting group or groups and, if desired, forming a salt.

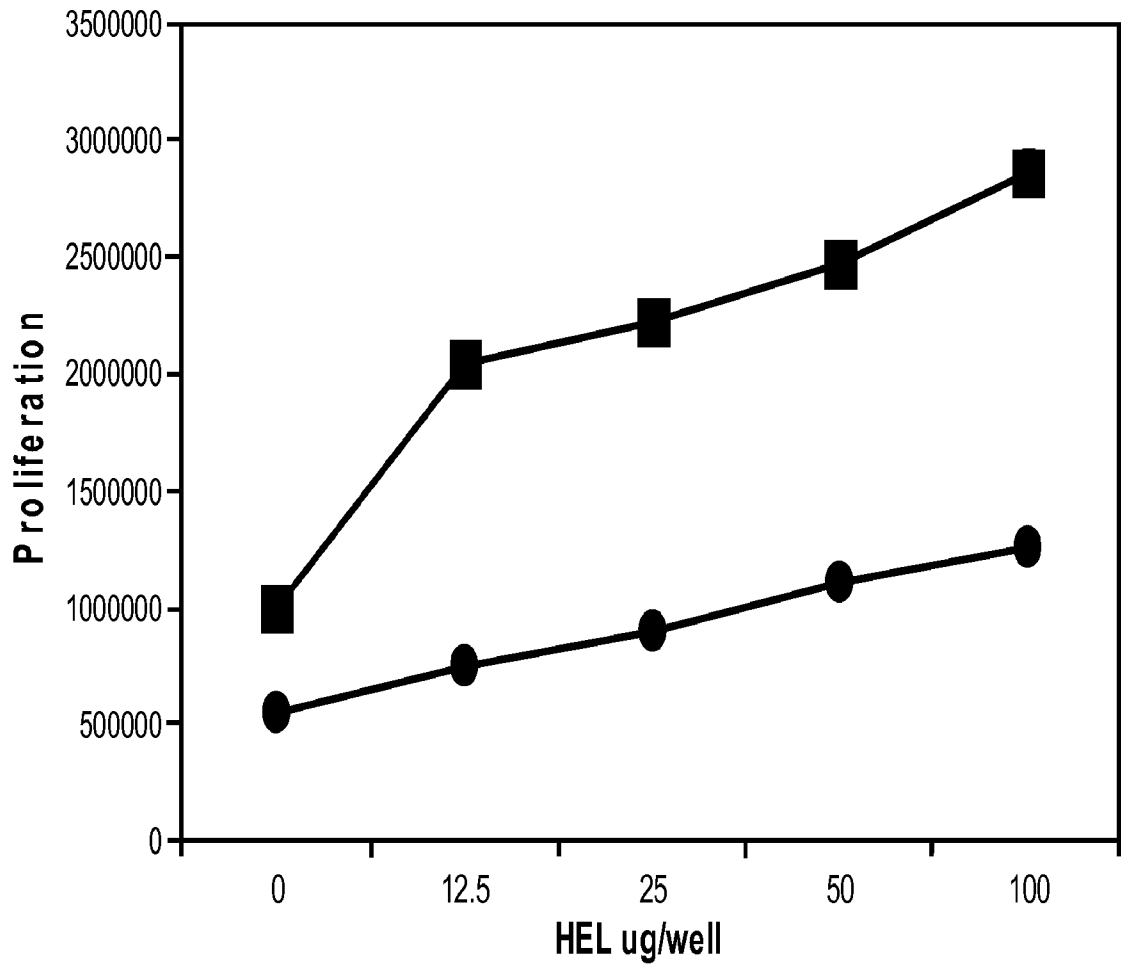


FIG. 1

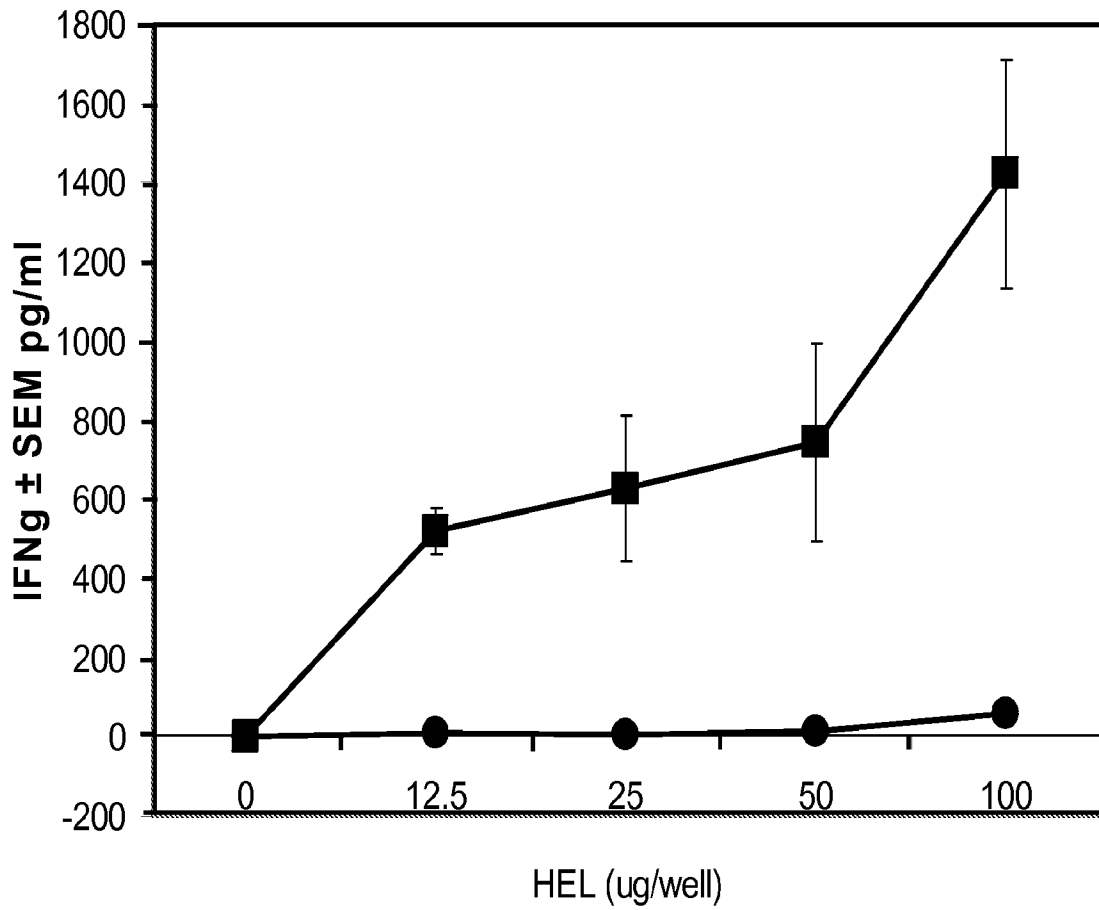


FIG. 2

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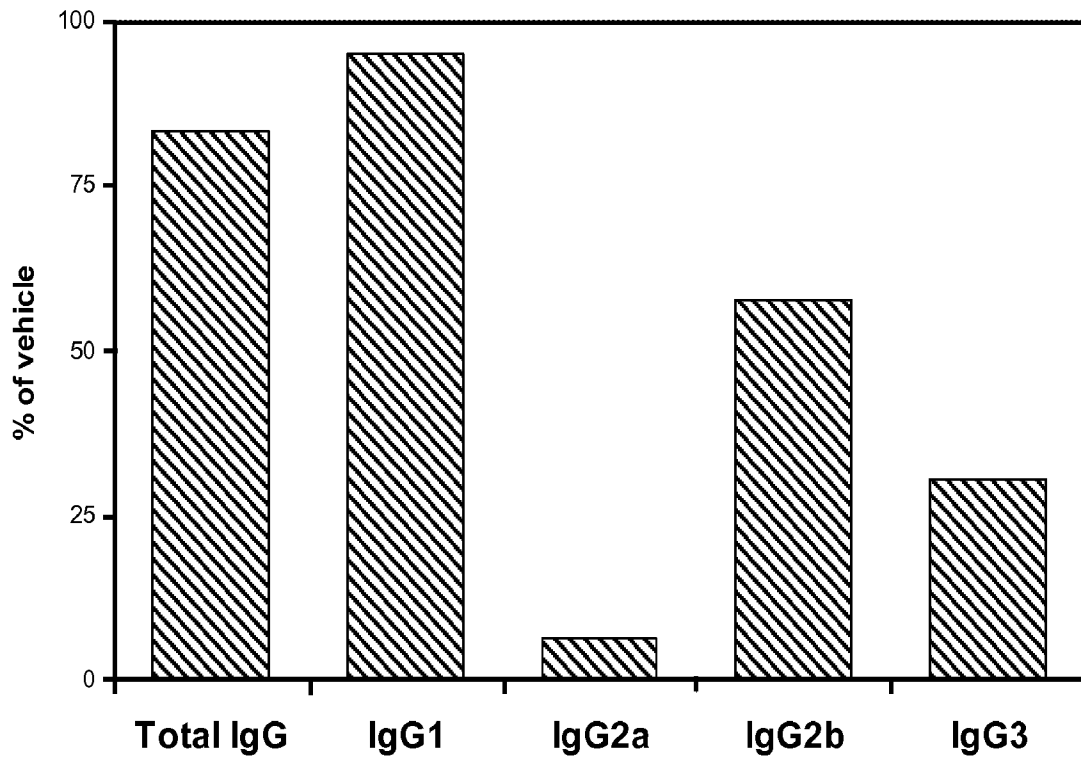


FIG. 3

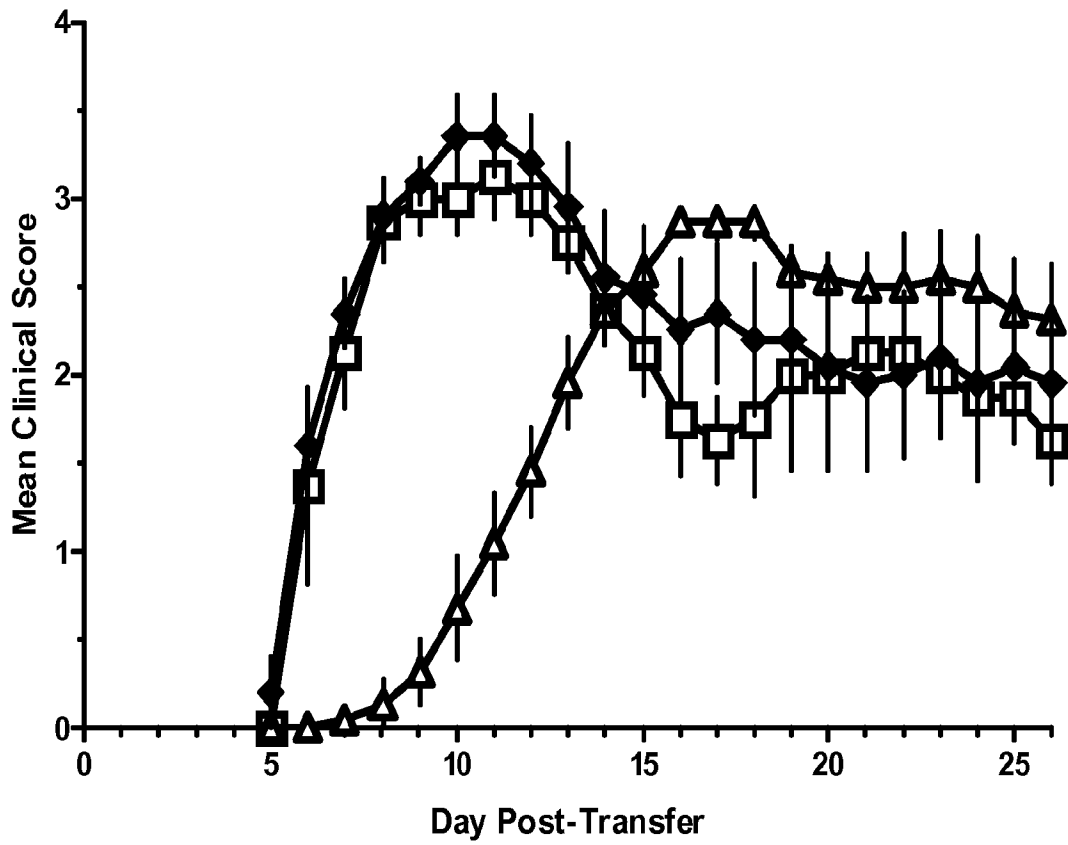


FIG. 4

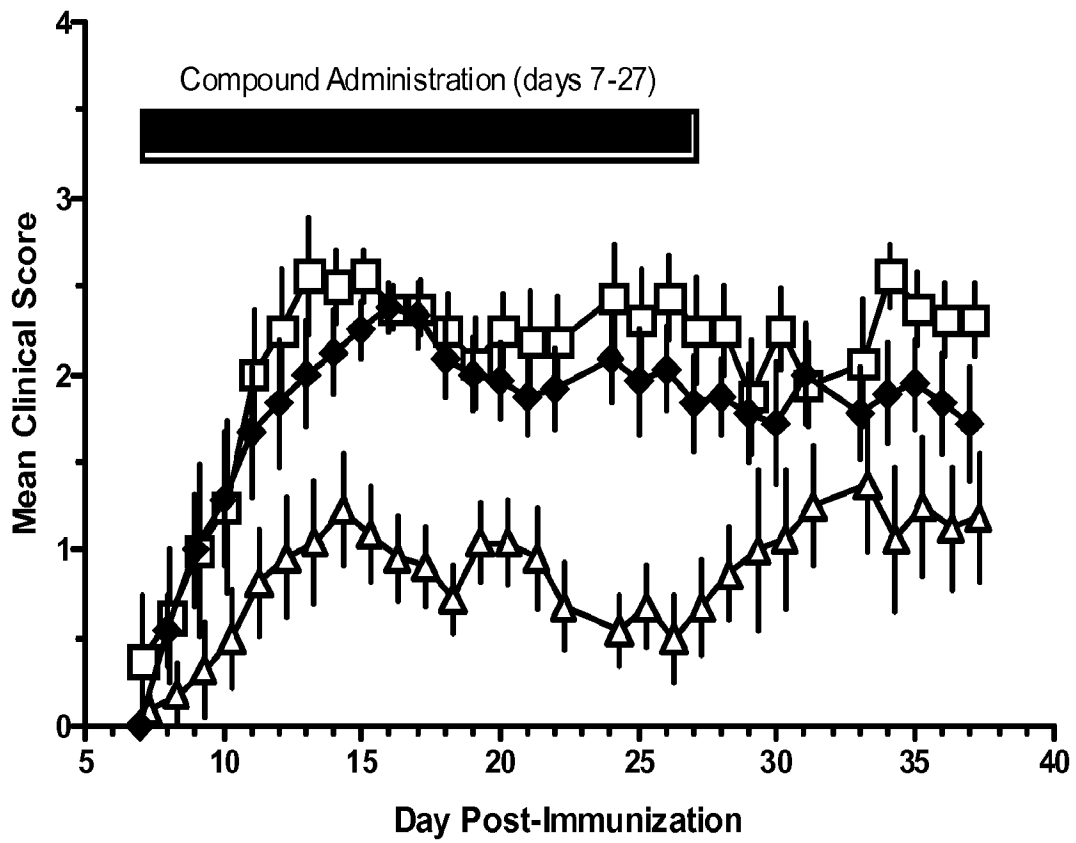


FIG. 5

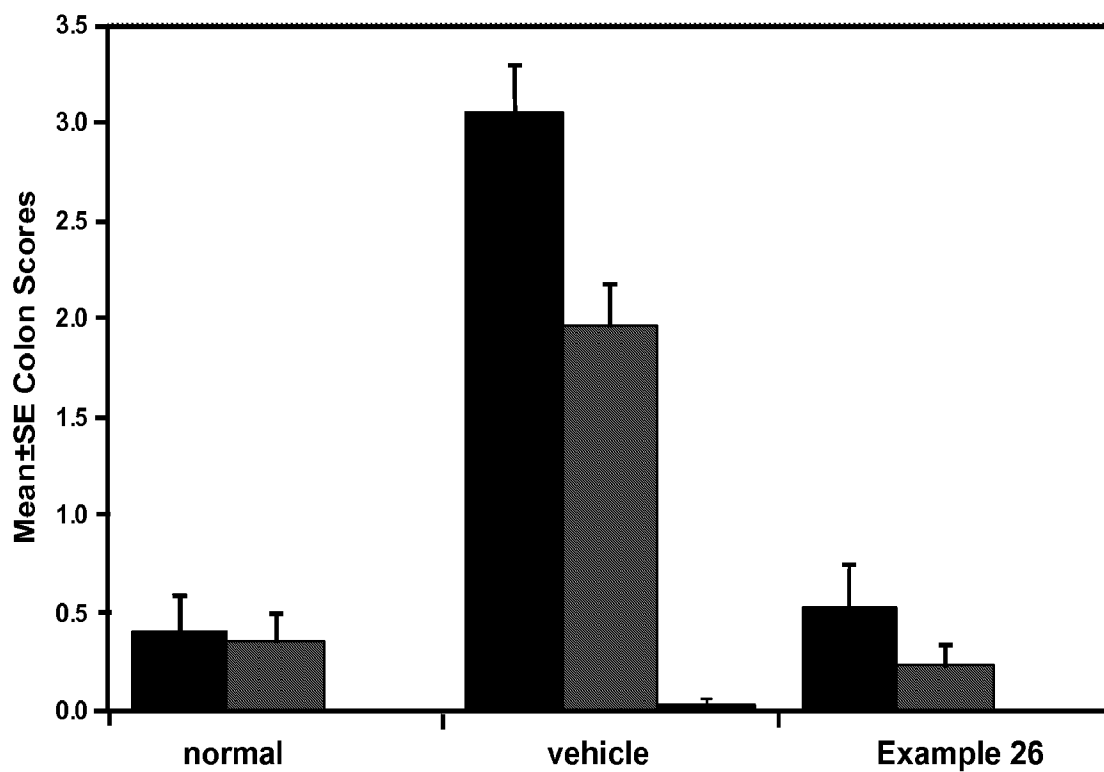


FIG. 6

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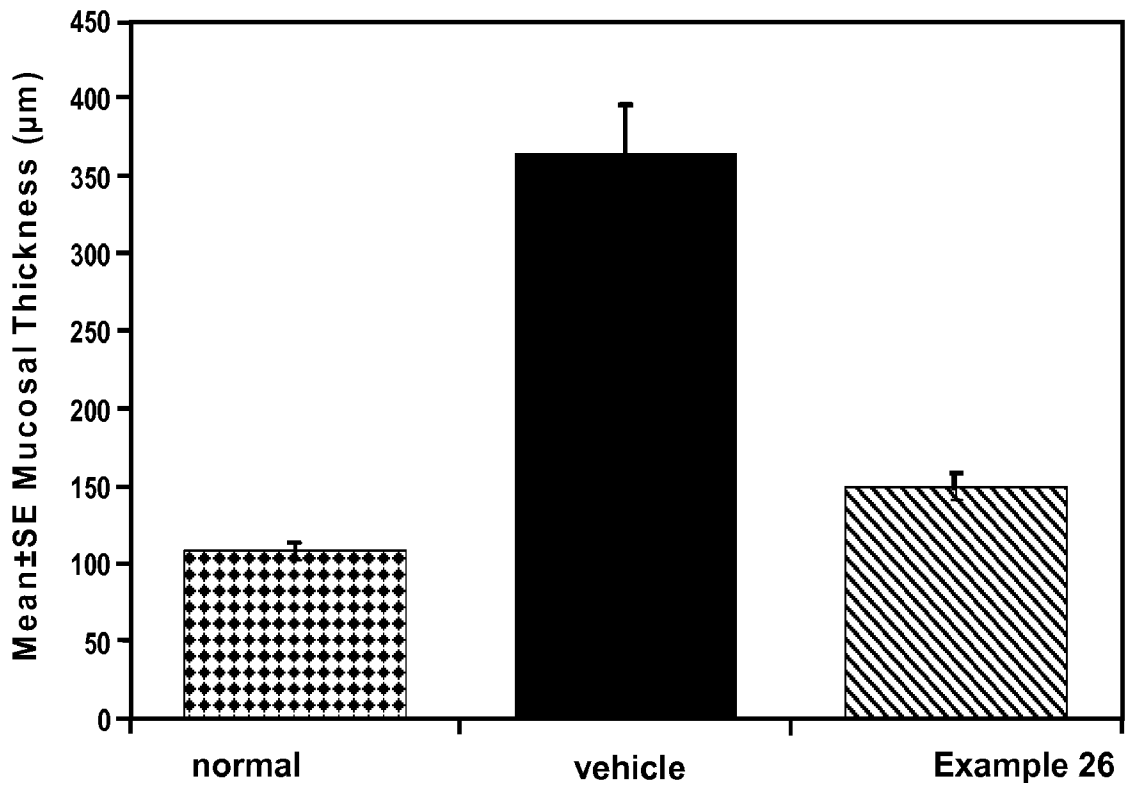


FIG. 7

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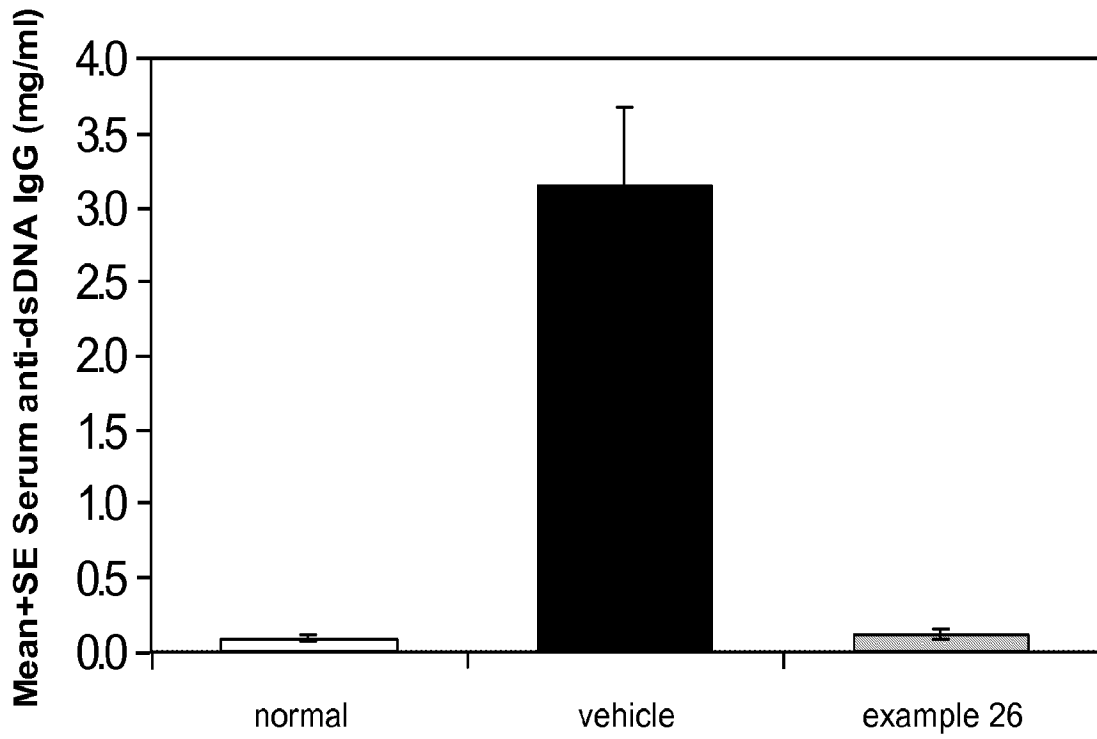


FIG. 8

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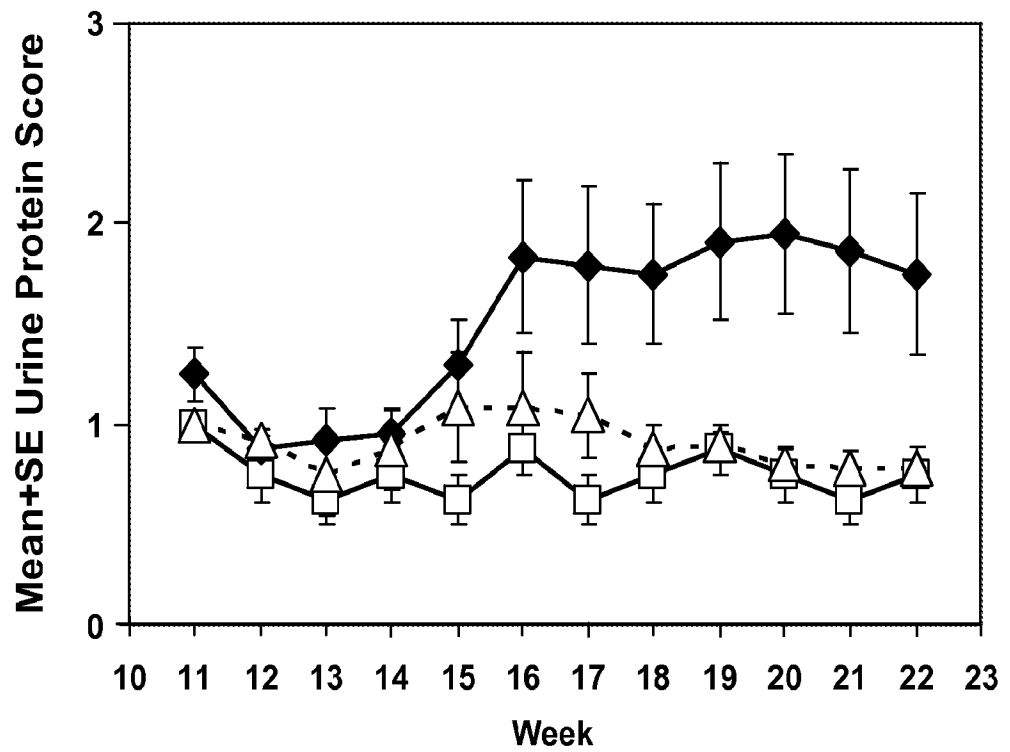


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/054193

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D471/04 A61K31/47		
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		
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 2007/173508 A1 (HUTCHINSON JOHN HOWARD [US] ET AL) 26 July 2007 (2007-07-26) compound with RN:944922-42-3 ((1,2,49-triazolo(4,3-a)quinoline, 7-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4-yl)phenoxy)methyl)-1-(2-quinolinyl)-); claims 1-22	1-36
A	US 2005/256309 A1 (ALTENBACH ROBERT J [US] ET AL) 17 November 2005 (2005-11-17) claims 1-12; example 3	1-36
P,A	WO 2008/121687 A2 (ARRAY BIOPHARMA INC [US]; MARMSAETER FREDRIK P [US]; MUNSON MARK C [US]) 9 October 2008 (2008-10-09) claims 1-32	1-36
----- -/--		
<input checked="" 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 :		
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