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(54) 5-Anilinoimidazopyridines and Methods of Use

5-Anilin-Imidazopyridine und Verfahren zu ihrer Verwendung

5-anilinoimidazopyridines et procédés d'utilisation

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(56) References cited:
WO-A-02/06213
WO-A-03/077855
US-A1- 2005 049 276
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Description

FIELD OF THE INVENTION

[0001] The invention relates to imidazopyridines with anti-cancer activity and more specifically to imidazopyridines which inhibit MEK kinase activity. The invention also relates to the medical uses of the compounds for the treatment of an inflammatory disease or for the inhibition of abnormal cell growth or for the treatment of a hyperproliferative disorder in a mammal.

BACKGROUND OF THE INVENTION

[0002] In the quest to understand how Ras transmits extracellular growth signals, the MAP (mitogen-activated protein) kinase (MAPK) pathway has emerged as the crucial route between membrane-bound Ras and the nucleus. The MAPK pathway encompasses a cascade of phosphorylation events involving three key kinases, namely Raf, MEK (MAP kinase kinase) and ERK (MAP kinase). Active GTP-bound Ras results in the activation and indirect phosphorylation of Raf kinase. Raf then phosphorylates MEK1 and 2 on two serine residues (S218 and S222 for MEK1 and S222 and S226 for MEK2) (Ahn et al., Methods in Enzymology 2001, 332, 417-431). Activated MEK then phosphorylates its only known substrates, the MAP kinases, ERK1 and 2. ERK phosphorylation by MEK occurs on Y204 and T202 for ERK1 and Y185 and T183 for ERK2 (Ahn et al., Methods in Enzymology 2001, 332, 417-431). Phosphorylated ERK dimerizes and then translocates to the nucleus where it accumulates (Khokhlatchev et al., Cell 1998, 93, 605-615). In the nucleus, ERK is involved in several important cellular functions, including but not limited to nuclear transport, signal transduction, DNA repair, nucleosome assembly and translocation, and mRNA processing and translation (Ahn et al., Molecular Cell 2000, 6,1343-1354). Overall, treatment of cells with growth factors leads to the activation of ERK1 and 2 which results in proliferation and, in some cases, differentiation (Lewis et al., Adv. Cancer Res. 1998, 74, 49-139).

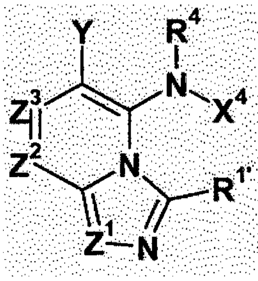
[0003] There has been strong evidence that genetic mutations and/or overexpression of protein kinases involved in the MAP kinase pathway lead to uncontrolled cell proliferation and, eventually, tumor formation, in proliferative diseases. For example, some cancers contain mutations which result in the continuous activation of this pathway due to continuous production of growth factors. Other mutations can lead to defects in the deactivation of the activated GTP-bound Ras complex, again resulting in activation of the MAP kinase pathway. Mutated, oncogenic forms of Ras are found in 50% of colon and >90% pancreatic cancers as well as many others types of cancers (Kohl et al., Science 1993,260, 1834-1837). Recently, bRaf mutations have been identified in more than 60% of malignant melanoma (Davies, H. et al., Nature 2002, 417, 949-954). These mutations in bRaf result in a constitutively active MAP kinase cascade. Studies of primary tumor samples and cell lines have also shown constitutive or overactivation of the MAP kinase pathway in cancers of pancreas, colon, lung, ovary and kidney (Hoshino, R. et al., Oncogene 1999, 18, 813-822).

[0004] MEK has emerged as an attractive therapeutic target in the MAP kinase cascade pathway. MEK, downstream of Ras and Raf, is highly specific for the phosphorylation of MAP kinase; in fact, the only known substrates for MEK-phosphorylation are the MAP kinases, ERK1 and 2. Inhibition of MEK has been shown to have potential therapeutic benefit in several studies. For example, small molecule MEK inhibitors have been shown to inhibit human tumor growth in nude mouse xenografts, (Sebolt-Leopold et al., Nature-Medicine 1999, 5 (7), 810-816); Trachet et al., AACR Apr. 6-10, 2002, Poster #5426; Tecle, H. IBC 2.sup.nd International Conference of Protein Kinases, Sep. 9-10, 2002), block static allodynia in animals (WO 01/05390 published Jan. 25, 2001) and inhibit growth of acute myeloid leukemia cells (Milella et al., J Clin Invest 2001, 108 (6), 851-859).

[0005] Several small molecule MEK inhibitors have also been discussed in, for example, WO 02/06213, WO 03/077855 and WO 03/077914. US 2005/153942 discloses MEK inhibitors which are based on pyrazolo-pyridines substituted by adjacent N-alkoxy-carboxamide groups and phenylamino groups. US 2005/049276 describes further MEK inhibitors based on imidazopyridines substituted by adjacent N-hydroxyalkyl-carboxamide and phenylamino groups. There still exists a need for new MEK inhibitors as effective and safe therapeutics for treating a variety of proliferative disease states, such as conditions related to the hyperactivity of MEK, as well as diseases modulated by the MEK cascade.

SUMMARY OF THE INVENTION

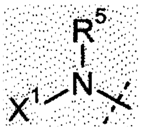
[0006] The invention relates generally to imidazopyridines as set out in the claims with anti-cancer and/or anti-inflammatory activity, and more specifically with MEK kinase inhibitory activity. Certain hyperproliferative and inflammatory disorders are characterized by the modulation of MEK kinase function, for example by mutations or overexpression of the proteins. Accordingly, the compounds named in the claims fall within the scope of Formula I and are useful in the treatment of hyperproliferative disorders such as cancer and/or inflammatory diseases such as rheumatoid arthritis.



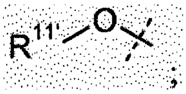
I

and salts thereof, wherein:

Z^1 is CR^1;
R^1 is H, C_1-C_3 alkyl, halo, CF_3, CHF_2, CN, OR^A or NR^AR^A;
$R^{1'}$ is H, C_1-C_3 alkyl, halo, CF_3, CHF_2, CN, OR^A, or NR^AR^A;
wherein each R^A is independently H or C_1-C_3 alkyl;
Z^2 is CR^2;
Z^3 is CR^3 or N;
R^2 and R^3 are independently selected from H, halo, CN, CF_3, $-OCF_3$, $-NO_2$, $-(CR^{14}R^{15})_nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nC(=Y')NR^{11}R^{12}$, $-(CR^{14}R1^{45})_nNR^{11}R^{12}$, $-(CR^{14}R^{15})_nOR^{11}$, $-CR^{14}R^{15})_nSR^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')R^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_nNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nOC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_nOP(=Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_n\ S(O)_2NR^{11}R^{12}$, $-(CR^{14}R^{15})_nS(O)(OR^{11})$, $-(CR^{14}R^{15})_nS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_n\ SC(=Y')R^{11}$, $-(CR^{14}R^{15})_nSC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nSC(=Y')NR^{11}R^{12}$, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl;
R^4 is H, C_1-C_6 alkyl or C_3-C_4 carbocyclyl;
Y is W-C(O)- or W';
W is



or

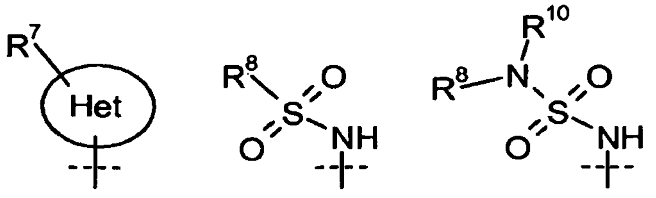


R^5 is H or C_1-C_{12} alkyl;
X^1 is selected from $R^{11'}$ and $-OR^{11'}$; when X^1 is $R^{11'}$, X^1 is optionally taken together with R^5 and the nitrogen atom to which they are bound to form a 4-7 membered saturated or unsaturated ring having 0-2 additional heteroatoms selected from O, S and N, wherein said ring is optionally substituted with one or more groups selected from halo, CN, CF_3, $-OCF_3$, $-NO_2$, oxo, $-(CR^{19}R^{20})_nC(=Y')R^{16}$, $-(CR^{19}R^{20})_n\ C(=Y')OR^{16}$, $-(CR^{19}R^{20})_nC(Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_n$-SR^{16}, $-(CR^{19}R^{20})_n\ NR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_n\ NR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_n\ NR^{18}C(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{17}SO^2R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nS(O)R^{16}$, $-(CR^{19}R^{20})_nS(O)_2R^{16}$, $-(CR^{19}R^{20})_nS(O)_2NR^{16}R^{17}$, $-(CR^{19}R^{20})n^{S}(O)(OR^{16})$, $-(CR^{19}R^{20})_n\ S(O)_2(OR^{16})$, $-(CR^{19}R^{20})_n\ SC(=Y')R^{16}$, $-(CR^{19}R^{20})_n\ SC(=Y')OR^{16}$, $-(CR^{19}R^{20})_n\ SC(=Y')NR^{16}R^{17}$, and R^{21};
each $R^{11'}$ is independently H, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl;
R^{11}, R^{12} and R^{13} are independently H, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl,
or R^{11} and R^{12} together with the nitrogen to which they are attached form a 3-8 membered saturated, unsaturated

or aromatic ring having 0-2 heteroatoms selected from O, S and N, wherein said ring is optionally substituted with one or more groups selected from halo, CN, CF_3, -CF3, NO_2, C_1-C_6 alkyl, -OH, -SH, -O(C_1-C_6 alkyl), -S(C_1-C_6 alkyl), $-NH_2$, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, $-SO_2$(C_1-C_6 alkyl), $-CO_2H$, $-CO_2$(C_1-C_6 alkyl), $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl, -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), NHC(O)(C_1-C_6 alkyl), $-NHSO_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)SO_2(C_1-C_6 alkyl), $-SO_2NH_2$, $-SO_2NH$(C_1-C_6 alkyl), $-SO_2N$(C_1-C_6 alkyl)$_2$, $-oC(O)NH_2$, -OC(O)NH(C_1-C_6 alkyl), -OC(O)N(C_1-C_6 alkyl)$_2$, -OC(O)O(C_1-C_6 alkyl), -NHC(O)NH(C_1-C_6 alkyl), NHC(O)N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)C(O)NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)N(C_1-C_6 alkyl)$_2$, NHC(O)NH(C_1-C_6 alkyl), -NHC(O)N(C_1-C_6 alkyl)$_2$, NHC(O)O(C_1-C_6 alkyl), and N(C_1-C_6 alkyl)C(O)O(C_1-C_6 alkyl);

R^{14} and R^{15} are independently selected from H, C_1-C_{12} alkyl, aryl, carbocyclyl, heterocyclyl, and heteroaryl;

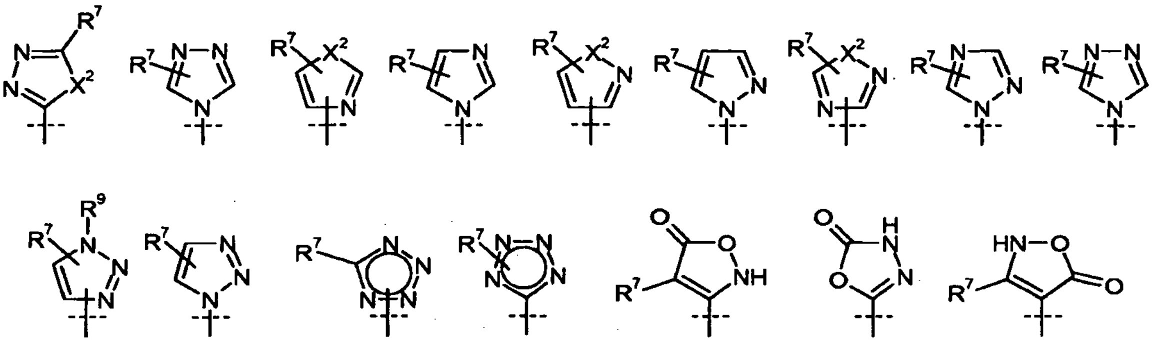
W' is



;

wherein

is



each X^2 is independently O, S, or NR^9;

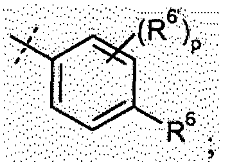
each R^7 is independently selected from H, halo, CN, CF_3, $-OCF_3$, NO_2, $-(CR^{14}R^{15})_nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nC(Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{11}R^{12}$, $-(CR^{14}R^{15})_nOR^{11}$, $-(CR^{14}R^{15})_nSR^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')R^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_nNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')OR^{11}$,$-(CR^{14}R^{15})_nOC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})nOP(-Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_n(O)_2R^{11}$, $-(CR^{14}R^{15})_n S(O)_2NR^{11}R^{12}$, $-(CR^{14}R^{15})_nS(O)(OR^{11})$, $-(CR^{14}R^{15})_nS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_n SC(=Y')R^{11}$, $-(CR^{14}R^{15})_nSC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nSC(=Y')NR^{11}R^{12}$, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl;

each R^8 is independently selected from C_1-C_{12} alkyl, aryl, carbocyclyl, heterocyclyl, and heteroaryl;

R^9 is selected from H, $-(CR^{14}R^{15})nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_qNR^{11}R^{12}$, $-(CR^{14}R^{15})_qOR^{11}$, $-(CR^{14}R^{15})_qSR^{11}$, $-(CR^{14}R^{15})_qNR^{12}C(=Y')R^{11}$, $-(CR^{14}R^{15})_qNR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_qNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_qNR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_qOC(=Y')R^{11}$, $-(CR^{14}R^{15})_qOC(=Y')OR^{11}$, $-(CR^{14}R^{15})_qOC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_qOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_qOP(=Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_qOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_n S(O)_2NR^{11}R^{12}$, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl;

R^{10} is H, C_1-C_6 alkyl or C_3-C_4 carbocyclyl;

X^4 is



R^6 is H, halo, C$_1$-C$_6$ alkyl, C$_2$-C$_8$ alkenyl, C$_2$-C$_8$ alkynyl, carbocyclyl, heteroaryl, heterocyclyl, -OCF$_3$, -NO$_2$, -Si(C$_1$-C$_6$ alkyl), -(CR^{19}R^{20})$_n$NR^{16}R^{17}, -(CR^{19}R^{20})$_n$OR^{16}, or -(CR^{19}R^{20})$_n$-SR^{16};
R$^{6'}$ is H, halo, C$_1$-C$_6$ alkyl, carbocyclyl, CF$_3$, -OCF$_3$, -NO$_2$, -Si(C$_1$-C$_6$ alkyl), -(CR^{19}R^{20})$_n$NR^{16}R^{17}, -(CR^{19}R^{20})$_n$OR^{16}, -(CR^{19}R^{20})$_n$-SR^{16}, C$_2$-C$_8$ alkenyl, C$_2$-C$_8$ alkynyl, heterocyclyl, aryl, or heteroaryl;
p is 0, 1,2 or 3;
n is 0, 1, 2 or 3;
q is 2 or 3;
wherein each said alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl of R^1, R^2, R^3, R^4, R^5, R^6, R$^{6'}$, R^7, R^8, R^9, R^{10}, R^{11}, R$^{11'}$, R^{12}, R^{13}, R^{14}, R^{15} and R^A is independently optionally substituted with one or more groups independently selected from halo, CN, CF$_3$, -OCF$_3$, -NO$_2$, oxo, -Si(C$_1$-C$_6$ alkyl)$_3$, -(CR^{19}R^{20})$_n$C(=Y')R^{16}, -(CR^{19}R^{20})$_n$ C(=Y')OR^{16}, -(CR^{19}R^{20})$_n$C(=Y')NR^{16}R^{17}, -(CR^{19}R)$_n$NR^{16}R^{17}, -(CR^{19}R^{20})$_n$OR^{16}, -(CR^{19}R^{20})$_n$SR^{16}, -(CR^{19}R^{20})$_n$NR^{16}C(=Y')R^{17}, -(CR^{19}R^{20})$_n$NR^{16}C(=Y')OR^{17}, -(CR^{19}R^{20})$_n$NR^{18}C(=Y')NR^{16}R^{17}, -(CR^{19}R^{20})$_n$NR^{17}SO$_2$R^{16},-(CR^{19}R^{20})$_n$OC(=Y')R^{16},
-(CR^{19}R^{20})$_n$OC(=Y')OR^{16},-(CR^{19}R^{20})$_n$OC(=Y')NR^{16}R^{17},-(CR^{19}R^{20})$_n$OS(O)$_2$(OR^{16}),
-(CR^{19}R^{20})$_n$OP(=Y')(OR^{16})(OR^{17}), -(CR^{19}R^{20})$_n$OP(OR^{16})(OR^{17}), -(CR^{19}R^{20})$_n$S(O)R^{16}, -(CR^{19}R^{20})$_n$S(O)$_2$R^{16}, -(CR^{19}R^{20})$_n$S(O)$_2$NR^{16}R^{17}, -(CR^{19}R^{20})nS(O)(OR^{16}), -(CR^{19}R^{20})$_n$ S(O)$_2$(OR^{16}), -(CR^{19}R^{20})$_n$SC(=Y')R^{16}, -(CR^{19}R^{20})$_n$SC(=Y')OR^{16}, -(CR^{19}R^{20})$_n$ SC(=Y')NR^{16}R^{17}, and R^{21};
each R^{16}, R^{17} and R^{18} is independently H, C$_1$-C$_{12}$ alkyl, C$_2$-C$_8$ alkenyl, C$_2$-C$_8$ alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein said alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more groups selected from halo, CN, -OCF$_3$, CF$_3$, -NO$_2$, C$_1$-C$_6$ alkyl, -OH, -SH, -O(C$_1$-C$_6$ alkyl), -S(C$_1$-C$_6$ alkyl), NH, -NH(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)$_2$, -SO$_2$(C$_1$-C$_6$ alkyl), -CO$_2$H, -CO$_2$(C$_1$-C$_6$ alkyl), -C(O)NH$_2$, -C(O)NH(C$_1$-C$_6$ alkyl), -C(O)N(C$_1$-C$_6$ alkyl)$_2$, -N(C$_1$-C$_6$ alkyl)C(O)(C$_1$-C$_6$ alkyl), -NHC(O)(C$_1$-C$_6$ alkyl), -NHSO$_2$(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)SO$_2$(C$_1$-C$_6$ alkyl), -SO$_2$NH$_2$, -SO$_2$NH(C$_1$-C$_6$ alkyl), -SO$_2$N(C$_1$-C$_6$ alkyl)$_2$,-OC(O)NH$_2$, -OC(O)NH(C$_1$-C$_6$ alkyl), -OC(O)N(C$_1$-C$_6$ alkyl)$_2$, -OC(O)O(C$_1$-C$_6$ alkyl), -NHC(O)NH(C$_1$-C$_6$ alkyl), NHC(O)N(C$_1$-C$_6$ alkyl)$_2$, -N(C$_1$-C$_6$ alkyl)C(O)NH(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)C(O)N(C$_1$-C$_6$ alkyl)$_2$, -NHC(O)NH(C$_1$-C$_6$ alkyl), -NHC(O)N(C$_1$-C$_6$ alkyl)$_2$, -NHC(O)O(C$_1$-C$_6$ alkyl), and -N(C$_1$-C$_6$ alkyl)C(O)O(C$_1$-C$_6$ alkyl);
or R^{16} and R^{17} together with the nitrogen to which they are attached form a 3-8 membered saturated, unsaturated or aromatic ring having 0-2 heteroatoms selected from O, S and N, wherein said ring is optionally substituted with one or more groups selected from halo, CN, -OCF$_3$, CF$_3$, -NO$_2$, C$_1$-C$_6$ alkyl, -OH, -SH, -O(C$_1$-C$_6$ alkyl), -S(C$_1$-C$_6$ alkyl), -NH$_2$, -NH(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)$_2$, -SO$_2$(C$_1$-C$_6$ alkyl), -CO$_2$H, -CO$_2$(C$_1$-C$_6$ alkyl), -C(O)NH$_2$, -C(O)NH(C$_1$-C$_6$ alkyl), -C(O)N(C$_1$-C$_6$ alkyl)$_2$, N(C$_1$-C$_6$alkyl)C(O)(C$_1$-C$_6$ alkyl), -NHC(O)(C$_1$-C$_6$ alkyl), -NHSO$_2$(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)SO$_2$(C$_1$-C$_6$ alkyl), -SO$_2$NH$_2$, -SO$_2$NH(C$_1$-C$_6$ alkyl), -SO$_2$N(C$_1$-C$_6$ alkyl)$_2$, -OC(O)NH$_2$, -OC(O)NH(C$_1$-C$_6$ alkyl), -OC(O)N(C$_1$-C$_6$ alkyl)$_2$, -OC(O)O(C$_1$-C$_6$ alkyl), -NHC(O)NH(C$_1$-C$_6$ alkyl), -NHC(O)N(C$_1$-C$_6$ alkyl)$_2$, -N(C$_1$-C$_6$ alkyl)C(O)NH(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)C(O)N(C$_1$-C$_6$ alkyl)$_2$, -NHC(O)NH(C$_1$-C$_6$ alkyl), -NHC(O)N(C$_1$-C$_6$ alkyl)$_2$, NHC(O)O(C$_1$-C$_6$ alkyl), and -N(C$_1$-C$_6$ alkyl)C(O)O(C$_1$-C$_6$ alkyl);
R^{19} and R^{20} are independently selected from H, C$_1$-C$_{12}$ alkyl, -(CH$_2$)$_n$-aryl, -(CH$_2$)$_n$-carbocyclyl, -(CH$_2$)$_n$-heterocyclyl, and -(CH$_2$)$_n$-heteroaryl;
R^{21} is C$_1$-C$_{12}$ alkyl, C$_2$-C$_8$ alkenyl, C$_2$-C$_8$ alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each member of R^{21} is optionally substituted with one or more groups selected from halo, oxo, CN, -OCF$_3$, CF$_3$, -NO$_2$, C$_1$-C$_6$ alkyl, -OH, -SH, -O(C$_1$-C$_6$ alkyl), -S(C$_1$-C$_6$ alkyl), -NH$_2$, NH(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)$_2$, -SO$_2$(C$_1$-C$_6$ alkyl), -CO$_2$H, -CO$_2$(C$_1$-C$_6$ alkyl), -C(O)NH$_2$, -C(O)NH(C$_1$-C$_6$ alkyl), -C(O)N(C$_1$-C$_6$ alkyl)$_2$, -N(C$_1$-C$_6$ alkyl)C(O)(C$_1$-C$_6$ alkyl), -NHC(O)(C$_1$-C$_6$ alkyl), -NHSO$_2$(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)SO$_2$(C$_1$-C$_6$ alkyl), -SO$_2$NH$_2$, -SO$_2$NH(C$_1$-C$_6$ alkyl), -SO$_2$N(C$_1$-C$_6$ alkyl)$_2$, -OC(O)NH$_2$, -OC(O)NH(C$_1$-C$_6$ alkyl), -OC(O)N(C$_1$-C$_6$ alkyl)$_2$, -OC(O)O(C$_1$-C$_6$ alkyl), -NHC(O)NH(C$_1$-C$_6$ alkyl), -NHC(O)N(C$_1$-C$_6$ alkyl)$_2$, -N(C$_1$-C$_6$ alkyl)C(O)NH(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)C(O)N(C$_1$-C$_6$ alkyl)$_2$, -NHC(O)NH(C$_1$-C$_6$ alkyl), -NHC(O)N(C$_1$-C$_6$ alkyl)$_2$, -NHC(O)O(C$_1$-C6 alkyl), and -N(C$_1$-C$_6$ alkyl)C(O)O(C$_1$-C$_6$ alkyl);
each Y' is independently O, NR^{22}, or S; and
R^{22} is H or C$_1$-C$_{12}$ alkyl.

[0007] The present invention includes a composition (e.g., a pharmaceutical composition) comprising a compound as set out in the claims and a carrier (a pharmaceutically acceptable carrier). The present invention also includes a composition (e.g., a pharmaceutical composition) comprising a compound of as set out in the claims and a carrier (a pharmaceutically acceptable carrier), further comprising a second chemotherapeutic and/or a second anti-inflammatory agent. The present compositions are useful for inhibiting abnormal cell growth or treating a hyperproliferative disorder in a mammal (e.g., human). The present compositions are also useful for treating inflammatory diseases in a mammal (e.g., human).

[0008] The present invention includes compounds of the present invention for use in a method of inhibiting abnormal cell growth or treating a hyperproliferative disorder in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound as set out in the claims
or a composition thereof, alone or in combination with a second chemotherapeutic agent.

[0009] The present invention includes compounds of the present invention for use in a method of treating an inflammatory disease in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound as set out in the claims or a composition thereof, alone or in combination with a second anti-inflammatory agent.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0010] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulae. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

DEFINITIONS

[0011] The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms. Examples of alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$),3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1 -butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-diethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, 1-heptyl, 1-octyl, and the like.

[0012] The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to twelve carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenyl radical includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include, but are not limited to, ethylenyl or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), and the like.

[0013] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of two to twelve carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond. Examples include, but are not limited to, ethynyl ($-C\equiv CH$), propynyl (propargyl, $-CH_2C\equiv CH$), and the like.

[0014] The terms "carbocycle", "carbocyclyl", "carbocyclic ring" and "cycloalkyl" refer to a monovalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms as a monocyclic ring or 7 to 12 carbon atoms as a bicyclic ring. Bicyclic carbocycles having 7 to 12 atoms can be arranged, for example, as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, and bicyclic carbocycles having 9 or 10 ring atoms can be arranged as a bicyclo [5,6] or [6,6] system, or as bridged systems such as bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Examples of monocyclic carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, and the like.

[0015] "Aryl" means a monovalent aromatic hydrocarbon radical of 6-18 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Some aryl groups are represented in the exemplary structures as "Ar". Aryl includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic or heterocyclic ring. Typical aryl groups include, but are not limited to, radicals derived from benzene (phenyl), substituted benzenes, naphthalene, anthracene, indenyl, indanyl, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like.

[0016] The terms "heterocycle," "heterocyclyl" and "heterocyclic ring" are used interchangeably herein and refer to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring) carbocyclic radical of 3 to 18 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen and sulfur, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described below. A heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, P, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. Heterocycles are described in Paquette, Leo A.; "Principles of Modem Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. "Heterocyclyl" also includes radicals where heterocycle radicals are fused with a saturated, partially unsaturated ring, or aromatic carbocyclic or heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinylimidazolinyl, imidazolidinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, and azabicyclo[2.2.2]hexanyl. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein ring atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1 -dioxo-thiomorpholinyl.

[0017] The term "heteroaryl" refers to a monovalent aromatic radical of 5- or 6-membered rings, and includes fused ring systems (at least one of which is aromatic) of 5-18 atoms, containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups are pyridinyl (including, for example, 2-hydroxypyridinyl), imidazolyl, imidazopyridinyl, pyrimidinyl (including, for example, 4-hydroxypyrimidinyl), pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0018] The heterocycle or heteroaryl groups may be carbon (carbon-linked) or nitrogen (nitrogen-linked) attached where such is possible. By way of example and not limitation, carbon bonded heterocycles or heteroaryls are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline.

[0019] By way of example and not limitation, nitrogen bonded heterocycles or heteroaryls are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline.

[0020] The term "halo" refers to F, Cl, Br or I. The heteroatoms present in heteroaryl or heterocyclcyl include the oxidized forms such as $N^+ \rightarrow O^-$, S(O) and $S(O)_2$.

[0021] The terms "treat" and "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the development or spread of cancer. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0022] The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can be measured, for example, by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

[0023] The terms "abnormal cell growth" and "hyperproliferative disorder" are used interchangeably in this application. "Abnormal cell growth", as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes, for example, the abnormal growth of: (1) tumor cells (tumors) that proliferate by expressing a mutated tyrosine kinase or overexpression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases in which aberrant tyrosine kinase activation occurs; (3) any tumors that proliferate by receptor tyrosine kinases; (4) any tumors that proliferate by aberrant serine/threonine kinase activation; and (5) benign and malignant cells of other proliferative diseases in which aberrant serine/threonine kinase activation occurs.

[0024] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. A "tumor" comprises one or more cancerous cells. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (*e.g.*, epithelial squamous cell cancer), lung cancer including small- cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, acute leukemia, as well as head/brain and neck cancer.

[0025] A chemotherapeutic agent" is a compound useful in the treatment of cancer. Examples of chemotherapeutic agents include Erlotinib (TARCEVA®, Genentech/OSI Pharm.), Bortezomib (VELCADE®, Millennium Pharm.), Fulvestrant (FASLODEx®, AstraZeneca), Sutent (SU11248, Pfizer), Letrozole (FEMARA®, Novartis), Imatinib mesylate (GLEEVEC®, Novartis), PTK787/ZK 222584 (Novartis), Oxaliplatin (Eloxatin®, Sanofi), 5-FU (5-fluorouracil), Leucovorin, Rapamycin (Sirolimus, RAPAMUNE®, Wyeth), Lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), Lonafarnib (SCH 66336), Sorafenib (BAY43-9006, Bayer Labs), and Gefitinib (IRESSA®, AstraZeneca), AG1478, AG1571 (SU 5271; Sugen), alkylating agents such as thiotepa and CYTOXAN® cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlomaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gamma1I and calicheamicin omegaI1 (Angew Chem. Intl. Ed. Engl. (1994) 33:183-186); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; antimetabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Illinois), and TAXOTERE® (doxetaxel; Rhône-Poulenc Rorer, Antony, France); chloranmbucil; GEMZAR® (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0026] Also included in the definition of chemotherapeutic agent" are: (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such As antiestrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors; (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Ralf and H-Ras; (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; a topoisomerase 1 inhibitor such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and (x) pharmaceutically acceptable salts, acids and derivatives of any of the above. Other anti-angiogenic agents include MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, COX-II (cyclooxygenase II) inhibitors, and VEGF receptor tyrosine kinase inhibitors. Examples of such useful matrix metalloproteinase inhibitors that can be used in combination with the present compounds/compositions (such as any one of the title compounds of EXAMPLES 5-25) are described in WO 96/33172, WO 96/27583, EP 818442, EP 1004578, WO 98/07697, WO 98/03516, WO 98/34918, WO 98/34915, WO 98/33768, WO 98/30566, EP 606,046, EP 931,788, WO 90/05719, WO 99/52910, WO 99/52889, WO 99/29667, WO 99/07675, EP 945864, U.S. Pat. No. 5,863,949, U.S. Pat. No. 5,861,510, and EP 780,386. Examples of VEGF receptor tyrosine kinase inhibitors include 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)- quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), and compounds such as those disclosed in PCT Publication Nos. WO 97/22596, WO 97/30035, WO 97/32856, and WO 98/13354).

[0027] Other examples of chemotherapeutic agents that can be used in combination with the present compounds (such as any one of the title compounds of EXAMPLES 5-25) include inhibitors of PI3K (phosphoinositide-3 kinase), such as those reported in Yaguchi et al (2006) Jour. of the Nat. Cancer Inst. 98(8):545-556; US 7173029; US 7037915; US 6608056; US 6608053; US 6838457; US 6770641; US 6653320; US 6403588; US 2008/0242665; WO 2006/046031; WO 2006/046035; WO 2006/046040; WO 2007/042806; WO 2007/042810; WO 2004/017950; US 2004/092561; WO 2004/007491; WO 2004/006916; WO 2003/037886; US 2003/149074; WO 2003/035618; WO 2003/034997; US 2003/158212; EP 1417976; US 2004/053946; JP 2001247477; JP 08175990; JP 08176070; US 6703414; and WO 97/15658. Specific examples of such PI3K inhibitors include SF-1126 (PT3 K inhibitor, Semafore Pharmaceuticals), BEZ-235 (PI3K inhibitor, Novartis), XL-147 (PI3K inhibitor, Exelixis, Inc.), and GDC-0941 (PI3K inhibitor, Genentech, Inc.).

[0028] The term "inflammatory diseases" as used in this application includes, but not limited to, rheumatoid arthritis, atherosclerosis, congestive hear failure, inflammatory bowel disease (including, but not limited to, Crohn's disease and ulcerative colitis), chronic obstructive pulmonary disease in the lung, fibrotic disease in the liver and kidney, Crohn's disease, lupus, skin diseases such as psoriasis, eczema and scleroderma, osteoarthritis, multiple sclerosis, asthma, diseases and disorders related to diabetic complications, fibrotic organ failure in organs such as lung, liver, kidney, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

[0029] An "anti-inflammatory agent" is a compound useful in the treatment of inflammation. Examples of anti-inflammatory agents include injectable protein therapeutics such as Enbrel®, Remicade®, Humira® and Kineret®. Other examples of anti-inflammatory agents include non-steroidal anti-inflammatory agents (NSAIDs), such as ibuprofen or aspirin (which reduce swelling and alleviate pain); disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate; 5-aminosalicylates (sulfasalazine and the sulfa-free agents); corticosteroids; immunomodulators such as 6-mercaptoputine ("6-MP"), azathioprine ("AZA"), cyclosporines, and biological response modifiers such as Remicade RTM. (infliximab) and Enbrel.RTM. (etanercept); fibroblast growth factors; platelet derived growth factors; enzyme blockers such as Arava.RTM. (leflunomide); and/or a cartilage protecting agent such as hyaluronic acid, glucosamine, and chondroitin.

[0030] A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as the MEK inhibitors disclosed herein and, optionally, a chemotherapeutic agent) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

[0031] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

[0032] The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0033] The term "stereoisomer" refers to compounds which have identical chemical constitution and connectivity, but different orientations of their atoms in space that cannot be interconverted by rotation about single bonds.

[0034] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as crystallization, electrophoresis and chromatography.

[0035] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0036] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S.* are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and 1 or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0037] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

[0038] The phrase "pharmaceutically acceptable salt" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the invention. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate "mesylate", ethanesulfonate, benzenesulfonate, p-toluenesulfonate, pamoate (i.e., 1.1'-methylene-bis -(2-hydroxy-3-naphthoate)) salts, alkali metal (e.g., sodium and potassium) salts, alkaline earth metal (e.g., magnesium) salts, and ammonium salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion.

[0039] If the compound of the invention is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[0040] If the compound of the invention is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include, but are not limited to, organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

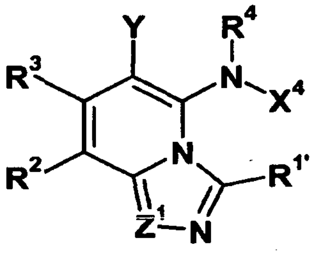
[0041] The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0042] A "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

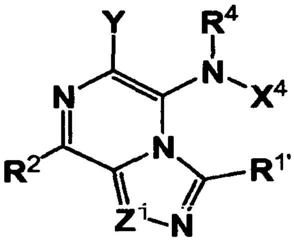
[0043] The term "protecting group" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and trialkylsilyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include phenylsulfonylethyl, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

[0044] The terms "compound of this invention", "compounds of the present invention" "imidazopyridines" and unless otherwise indicated, include compounds/imidazopyridines as set out in the claims and stereoisomers, geometric isomers, tautomers, solvates, metabolites, salts (e.g., pharmaceutically acceptable salts) and prodrugs thereof.-$(CR^{14}R^{15})_nS(O)_2R^{11}$; n is 0; and Z^1 is N, then said R^{11} or R^{12} is not aryl; when Z^1 is N, then R^3 is not CH_2-aryl; and all other variables are as defined in formula I.

[0045] In an embodiment of the present invention, compounds are of formula I-a or I-b and all other variables are as defined in formula I, or as defined in the embodiment described above.



I-a



I-b

[0046] In an embodiment of the present invention, R^2 is H, halo, CF_3, or C_1-C_3 alkyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments described above.

[0047] In another embodiment of the present invention, R^2 is H, methyl, CF_3, F, or Cl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments described above.

[0048] In another embodiment of the present invention, R^2 is H, F or Cl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments described above.

[0049] In an embodiment of the present invention, R^3 is H, halo, CF_3, or C_1-C_3 alkyl; and all other variables are as defined in formula I or I-a, or as defined in any one of the embodiments described above.

[0050] In another embodiment of the present invention, R^3 is H, methyl, CF_3, F, or Cl; and all other variables are as defined in formula I or I-a, or as defined in any one of the embodiments described above.

[0051] In another embodiment of the present invention, R^3 is H, F or Cl; and all other variables are as defined in formula I or I-a, or as defined in any one of the embodiments described above.

[0052] In an embodiment of the present invention, R^1 is H or C_1-C_3 alkyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments described above. In another embodiment, $R^{1'}$ is H, and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments described above.

[0053] In an embodiment of the present invention, Z^1 is CR^1 and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments described above.

[0054] In an embodiment of the present invention, Z^1 is N and all other variables are as defined in formula I or I-a, or as defined in any one of the embodiments described above.

[0055] In another embodiment of the present invention, Z^1 is CR^1 and R^1 is H or C_1-C_3 alkyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments described above. In another embodiment, R^1 is H, and all other variables arc as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above. In another embodiment, R^1 is methyl, and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0056] In an embodiment of the present invention, R^4 is H or C_1-C_6 alkyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0057] In another embodiment of the present invention, R^4 is H or methyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above. In another embodiment of the present invention, R^4 is H; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0058] In an embodiment of the present invention, R^5 is H or C_1-C_6 alkyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0059] In another embodiment of the present invention, R^5 is H or methyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0060] In another embodiment of the present invention, R^5 is H; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0061] In another embodiment of the present invention, R^5 is methyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

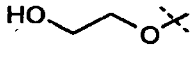
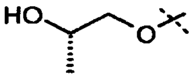
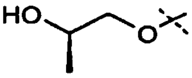
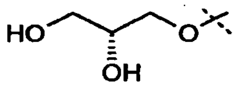
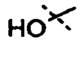
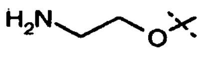
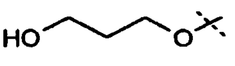
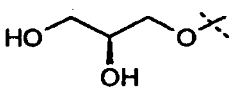
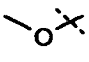
[0062] In an embodiment of the present invention, X^1 is $OR^{11'}$; and all other variables are as defined in formula I, I-a or I-b; or as defined in any one of the embodiments above.

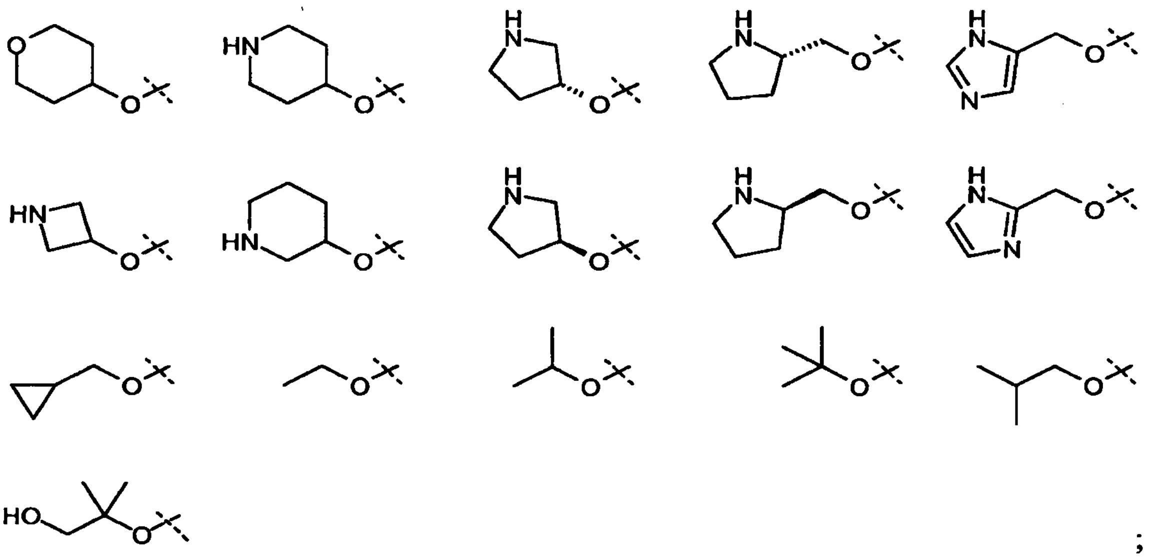
[0063] In another embodiment of the present invention, X^1 is $OR^{11'}$ wherein $R^{11'}$ is H or C_1-C_{12} alkyl (e.g., C_1-C_6 alkyl) substituted with one or more groups independently selected from halo, CN, CF_3, $-OCF_3$, $-NO_2$, oxo, $-(CR^{19}R^{2o})_n C(=Y')R^{16}$, $-(CR^{19}R^{20})_nC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})nOR^{16}$, $-(CR^{19}R^{20})_nSR^{16}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_n NR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_nNR^{18}C(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{17}SO_2R^{16}$,$-(CR^{19}R^{20})_nOC(=Y')R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nS(O)R^{16}$, $-(CR^{19}R^{20})_nS(O)_2R^{16}$, $-(CR^{19}R^{20})_nS(O)_2NR^{16}R^{17}$, $-(CR^{19}R^{20})_nS(O)(OR^{16})$, $-(CR^{19}R^{20})_nS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_n SC(=Y')R^{16}$,$-(CR^{19}R^{20})_nSC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nSC(=Y')NR^{16}R^{17}$, and R^{21}; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0064] In another embodiment of the present invention, X^1 is $OR^{11'}$ wherein $R^{11'}$ is heterocyclyl (e.g., 4- to 6-membered heterocyclyl) optionally substituted with one or more groups independently selected from halo, CN, CF_3, $-OCF_3$, $-NO_2$, oxo, $-(CR^{19}R^{20})_nC(=Y')R^{16}$,$-CR^{19}R^{20})_nC(=Y')OR^{16}$,$-(CR^{19}R^{20})_nC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_nSR^{16}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_nNR^{18}C(=Y')NR^{16}R^{17}$,$-(CR^{19}R^{20})_nNR^{17}SO_2R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nS(O)R^{16}$,$-(CR^{19}R^{20})_nS(O)_2R^{16}$,$-(CR^{19}R^{20})_nS(O)_2NR^{16}R^{17}$, $-(CR^{19}R^{20})_nS(O)(OR^{16})$, $-(CR^{19}R^{20})_n S(O)_2(OR^{16})$, $=(CR^{19}R^{20})_nSC(=Y')R^{16}$, $-(CR^{19}R^{20})_nSC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nSC(=Y')NR^{16}R^{17}$, and R^{21}; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0065] In another embodiment of the present invention, X^1 is $OR^{11'}$ wherein R^{11} is 4-to 6-membered heterocyclyl having 1 nitrogen ring atom wherein said heterocyclyl is optionally substituted with one or more groups independently selected from halo, CN, CF_3, $-OCF_3$, $-NO_2$, oxo, $-(CR^{19}R^{20})_nC(=Y')R^{16}$, $-(CR^{19}R^{20})_nC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_nSR^{16}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_n NR^{18}C(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{17}SO_2R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')R^{16}$,$-(CR^{19}R^{20})_nOC(=Y')OR^{16}$,$-(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nS(O)R^{16}$, $-(CR^{19}R^{20})_nS(O)_2R^{16}$, $-(CR^{19}R^{20})_nS(O)_2NR^{16}R^{17}$, $-(CR^{19}R^{20})_nS(O)(OR^{16})$, $-(CR^{19}R^{20})_n S(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nSC(=Y')R^{16}$, $-(CR^{19}R^{20})_nSC(=Y')OR^{16}$, $-(CR^{19}R^{20})_n SC(=Y')NR^{16}R^{17}$, and R^{21}; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0066] In another embodiment of the present invention, X^1 is:

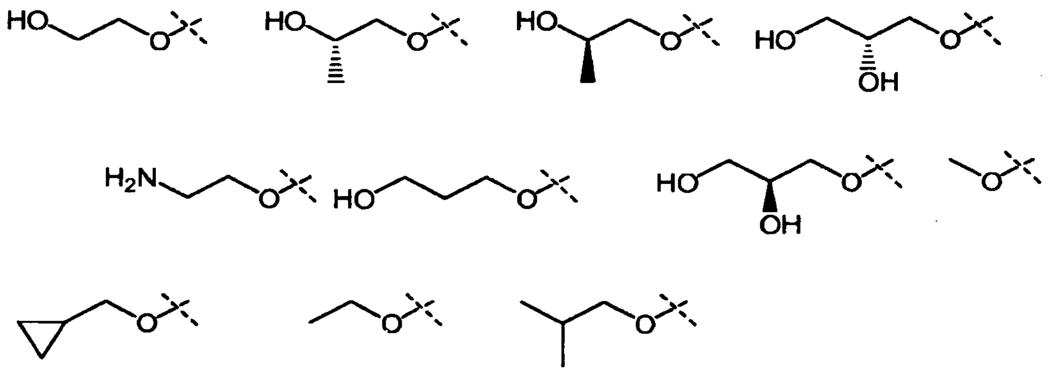












;

and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0067] In another embodiment of the present invention, X^1 is



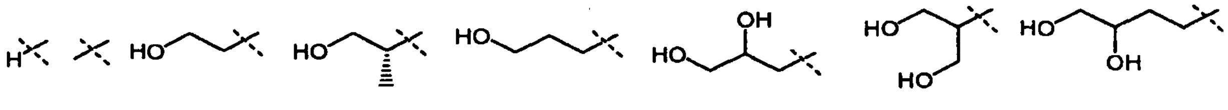
;

and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0068] In an embodiment of the present invention, X^1 is $R^{11'}$; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0069] In another embodiment of the present invention, X^1 is $R^{11'}$ wherein $R^{11'}$ is H or C_1-C_{12} alkyl (e.g., C_1-C_6 alkyl) substituted with one or more groups independently selected from halo, CN, CF_3, $-OCF_3$, NO_2, oxo, $-Si(C_1$-C_6 alkyl), $-(CR^{19}R^{20})_n$ $C(=Y')R^{16}$, $-(CR^{19}R^{20})_nC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nC(=Y')NR^{16}R^{17}$,$-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_nSR^{16}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_n$ $NR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_nNR^{18}C(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{17}SO_2R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')OR^{16}$,$-(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nS(O)R^{16}$, $-(CR^{19}R^{20})_nS(O)_2R^{16}$, $-(CR^{19}R^{20})_n$ $S(O)_2NR^{16}R^{17}$, $-(CR^{19}R^{20})_nS(O)(OR^{16})$, $-(CR^9R^{20})_nS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_n$ $SC(=Y')R^{16}$, $-(CR^{19}R^{20})_nSC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nSC(=Y')NR^{16}R^{17}$, and R^{21}; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0070] In another embodiment of the present invention, X^1 is

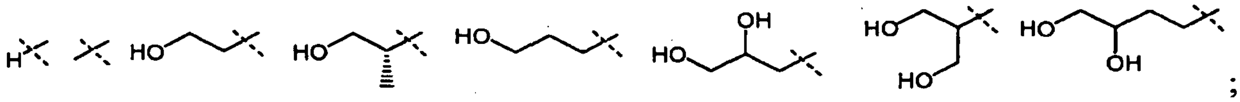


;

and

all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

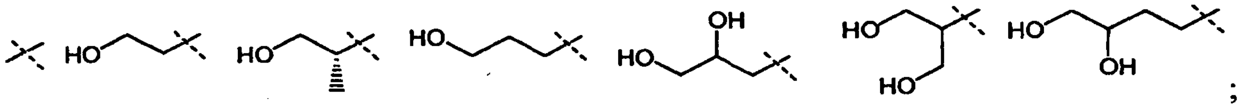
[0071] In another embodiment of the present invention, R^5 is H and X^1 is



and

all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

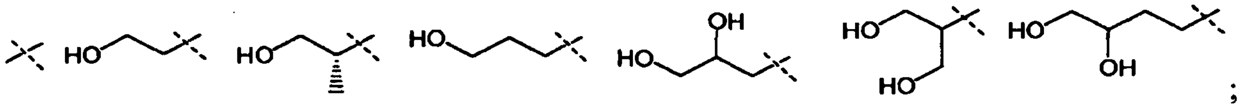
[0072] In another embodiment of the present invention, X^1 is



and

all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

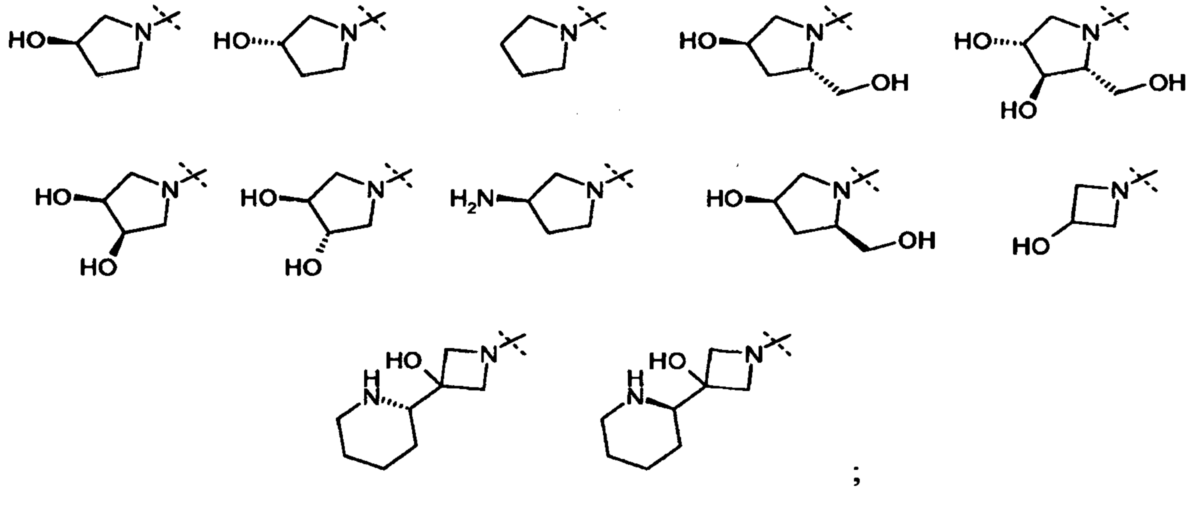
[0073] In another embodiment of the present invention, R^5 is methyl and X^1 is



and all other variables are as defmed in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0074] In an embodiment of the present invention, X^1 is R^{11} and X^1 is taken together with R^5 and the nitrogen atom to which they are bound to form a 4-5 membered saturated cyclic ring having 0-2 additional heteroatoms selected from O, S and N, wherein said cyclic ring is optionally substituted with one or more groups selected from halo, CN, CF_3, $-OCF_3$, $-NO_2$, oxo, $-(CR^{19}R^{20})_nC(=Y')R^{16}$, $-(CR^{19}R^{20})_n C(=Y')OR^{16}$, $-(CR^{19}R^{20})_nC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_n-SR^{16}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_n NR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_n NR^{18}C(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{17}SO_2R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, $-(CR^{15}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $(CR^{19}R^{20})_nS(O)R^{16}$, $-(CR^{19}R^{20})_nS(O)_2R^{16}$, $-(CR^{19}R^{20})_nS(O)_2NR^{16}R^{17}$, $-(CR^{19}R^{20})_nS(O)(OR^{16})$, $-(CR^{19}R^{20})_n S(O)_2(OR^{16})$, $-(CR^{19}R^{20})_n SC(=Y')R^{16}$, $-(CR^{19}R^{20})_n SC(=Y')OR^{16}$, $-(CR^{19}R^{20})_n SC(=Y')NR^{16}R^{17}$, and R^{21}; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0075] In another embodiment of the present invention, W is:



and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0076] In an embodiment of the present invention, W is $-OR^{11'}$ wherein $R^{11'}$ is H or C_1-C_{12} alkyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0077] In another embodiment of the present invention, W is $-OR^{11'}$ wherein $R^{11'}$ is H; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0078] In another embodiment of the present invention, W is -OR$^{11'}$ wherein R$^{11'}$ is C_1-C_6 alkyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0079] In an embodiment of the present invention, W' is $NHSO_2R^8$; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

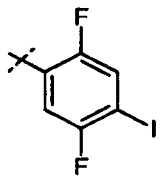
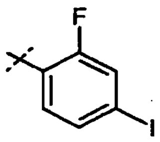
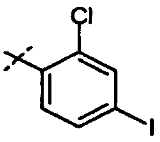
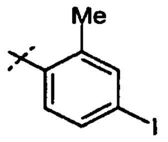
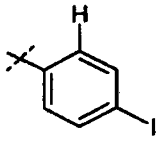
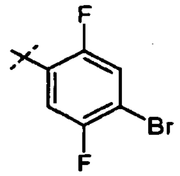
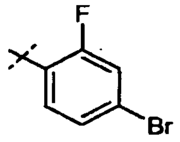
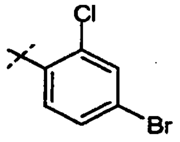
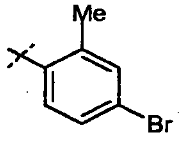
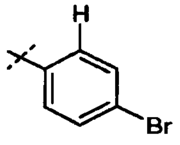
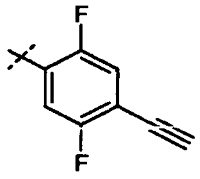
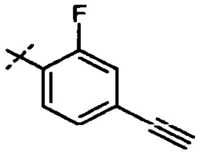
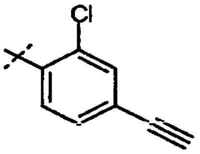
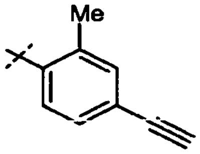
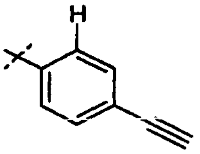
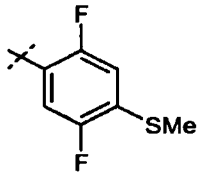
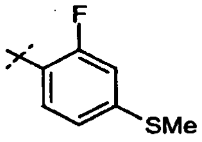
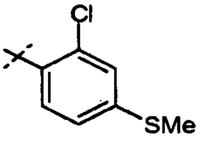
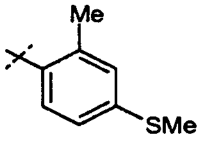
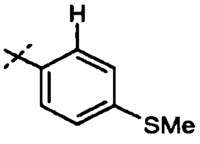
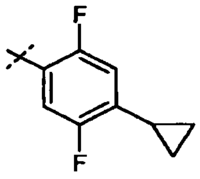
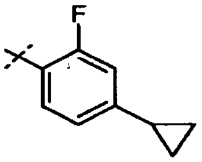
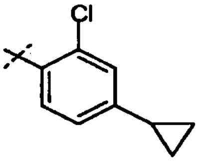
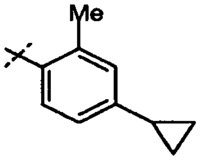
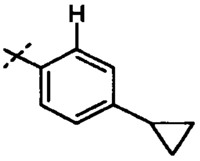
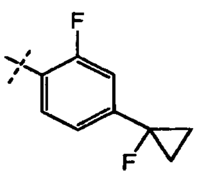
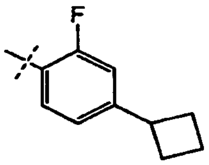
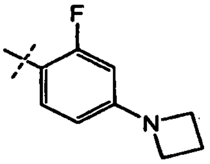
[0080] In an embodiment of the present invention, R^6 is halo, C_2-C_8 alkynyl, carbocyclyl, or -SR^{16}; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0081] In another embodiment of the present invention, R^6 is halo, C_2-C_3 alkynyl, C_3-carbocyclyl, or -SR^{16} wherein R^{16} is C_1-C_2 alkyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0082] In an embodiment of the present invention, $R^{6'}$ is H, halo, or C_1-C_3 alkyl; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0083] In an embodiment of the present invention, p is 1 or 2; and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0084] In another embodiment of the present invention, X^4 is

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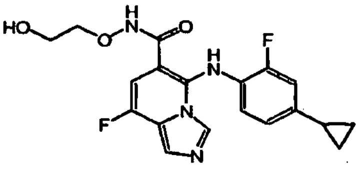
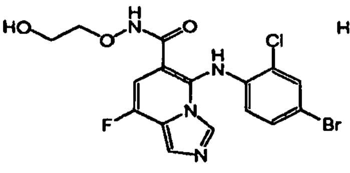
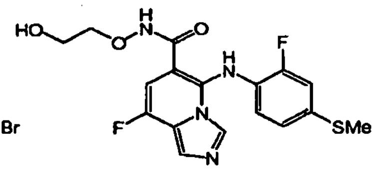
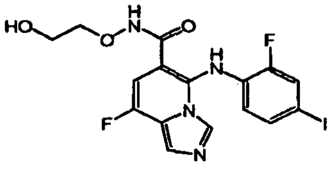
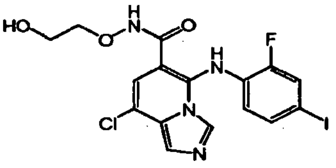
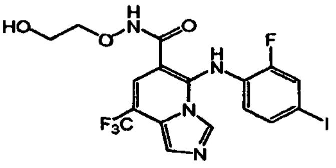
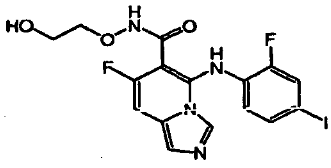
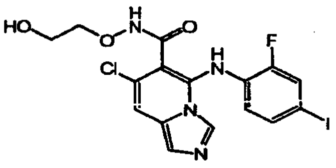
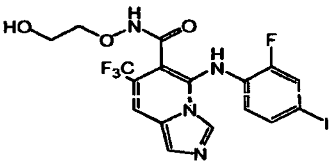
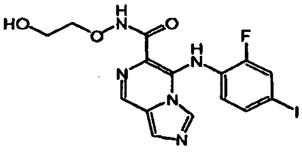
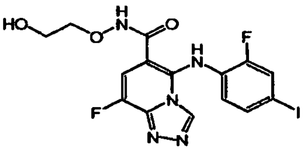
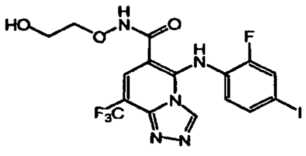
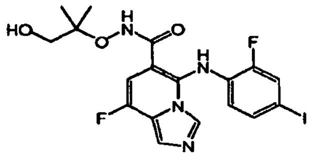
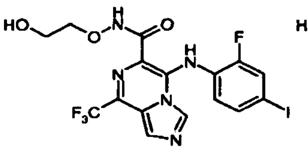
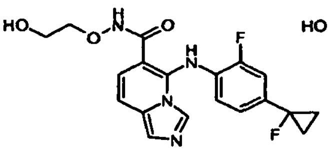
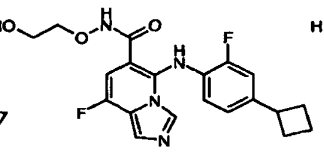
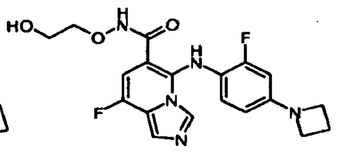
and all other variables are as defined in formula I, I-a or I-b, or as defined in any one of the embodiments above.

[0085] In another embodiment of the present invention, X^4 is

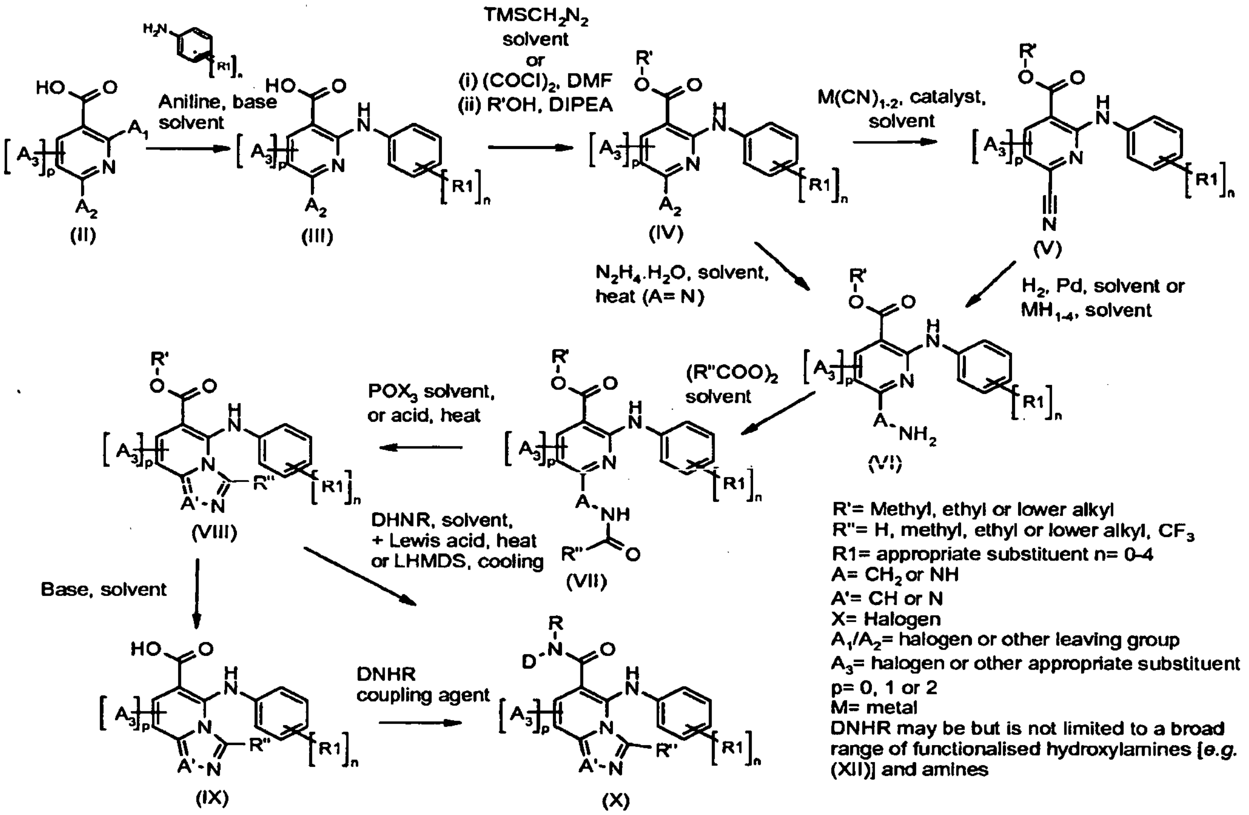
[0086] Another embodiment of the present invention includes compounds described in EXAMPLES 5-25 and compounds below:

Preparation of Compounds of formula I

[0087] The imidazopyridines of formula I are prepared according to the procedures described below in the schemes and examples or by methods known in the art. For example, compounds of formula (I) where Y= W-C(O)- may be prepared according to Scheme 1.

Scheme 1



R'= Methyl, ethyl or lower alkyl
R''= H, methyl, ethyl or lower alkyl, CF_3
R1= appropriate substituent n= 0-4
A= CH_2 or NH
A'= CH or N
X= Halogen
A_1/A_2= halogen or other leaving group
A_3= halogen or other appropriate substituent
p= 0, 1 or 2
M= metal
DNHR may be but is not limited to a broad range of functionalised hydroxylamines [*e.g.* (XII)] and amines

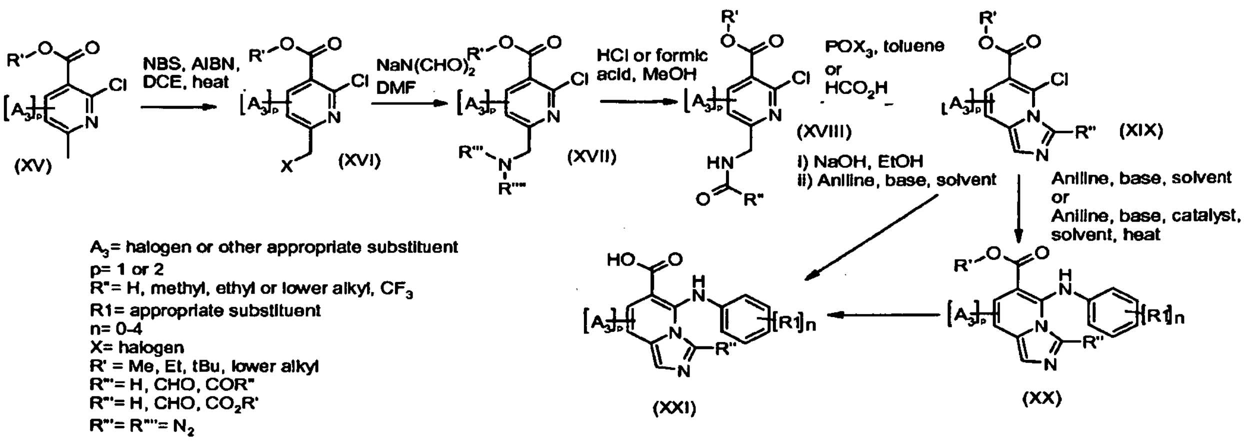
[0088] Nicotinic acids of formula (II) may be obtained commercially or prepared using methods described in the literature. The acids (II) may be reacted with anilines (incorporating appropriate substituents R1), in the presence of a base such as LiHMDS, in a solvent such as THF, at a temperature of from -78°C to 25°C to give acids of formula (III). Nicotinic esters (IV) may be prepared from nicotinic acids (III) by reaction with an alkylating agent such as trimethylsilyl diazomethane in a solvent such as toluene, at a temperature of from 0°C to 50°C. 2-Anilino-6-cyanopyridines of formula (V) may be prepared from 6-halo pyridines (IV) by reaction with an inorganic cyanide such as zinc cyanide, in the presence of a transition metal catalyst such as $Pd(PPh_3)_4$, in a solvent such as DMF, at a temperature of from 50°C to reflux temperature, or under microwave irradiation at a temperature of from 70°C to 200°C. Cyanopyridines (V) may be reduced to give 2-aminomethyl pyridines (VI), A= CH_2, by reduction with hydrogen at a pressure of from 1 to 5 atmospheres, in the presence of a catalyst such as palladium on carbon, in a solvent such as methanol or acetic acid, with or without added strong acid such as concentrated hydrochloric acid. Alternatively, the cyanopyridines (V) may be converted to 2-aminomethyl pyridines by reacting with an inorganic metal hydride such as sodium borohydride, in the presence of a metal salt such as cobalt chloride, in a solvent such as methanol, at a temperature of from 0°C to room temperature. Alternatively compounds of formula (VI), A= NH, may be prepared from compounds of formula (IV) by reaction with hydrazine hydrate, in a solvent such as ethanol, at a temperature of from 0°C to reflux.

[0089] Compounds (VII) may be prepared from compounds (VI) by reaction with an anhydride such as acetic anhydride, or mixed anhydride such as formic-acetic anhydride, in a solvent such as tetrahydrofuran, at a temperature of from 0°C to reflux. Compounds of formula (VIII) may be prepared from compounds (VII) by reaction with a chlorinating agent such as phosphorous oxychloride, in a solvent such as toluene, at a temperature of from 25°C to reflux. Alternatively compounds of formula (VIII) may be prepared from compounds of formula (VII) by reaction with an acid such as formic acid, neat or in a solvent such as dioxane, at a temperature of from 50°C to reflux. Compounds of formula (IX) can be obtained from compounds of formula (VIII) by reaction with a base such as sodium hydroxide, in a solvent such as ethanol or methanol, at a temperature of from room temperature up to reflux temperature.

[0090] Compounds of formula (IX) can be reacted with a functionalised hydroxylamine of formula (XII) (commercially available or prepared according to Scheme 5, 6 and 7) or an amine, and a suitable coupling agent, such as *O*-(7-aza-benzo-triazol-1-yl)-*N,N,N',N'*-tetra-methyluronium hexafluoro-phosphate, *N*-(3-dimethylaminopropyl)-*N'*- ethylcarbodiimide hydrochloride or *N,N'*-dicyclohexylcarbodiimide in the presence of *N*- hydroxy-1,2,3-benzotriazole, in the presence of a suitable base such as diisopropylethylamine or triethylamine in an inert solvent, such as tetrahydrofuran, *N,N*-dimethylformamide, or dichloromethane at a temperature of about room temperature, to obtain the compounds of formula (X). Compounds of formula (X) can be obtained directly from compounds of formula (VIII) by reaction with an amine or hydroxylamine DNHR in the presence of a Lewis acid such as trimethyl aluminium, in a solvent such as DCM, at a temperature of from room temperature up to reflux temperature. Alternatively, compounds of formula (X) may be prepared from compounds of formula (VIII) by treatment with a functionalized hydroxylamine in the presence of a base such as lithium bis(trimethylsilyl)amide in a solvent such as THF at a temperature of from -78°C to 25°C.

[0091] Additionally, compounds of formula (I) where Y is W-C(O)- may be prepared according to Scheme 2.

Scheme 2

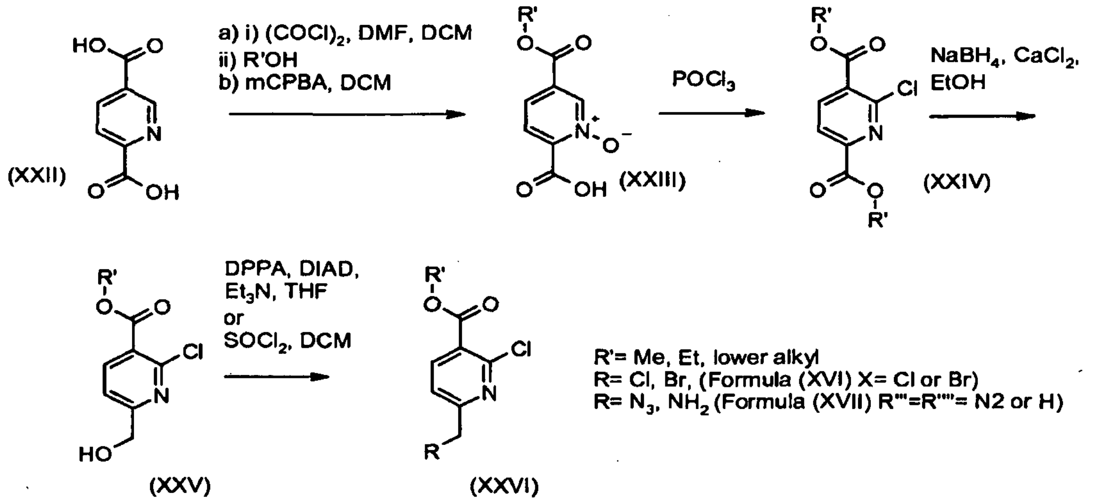


[0092] Compounds of formula (XV) may be obtained commercially or prepared using methods described in the literature. Compounds of formula (XVI) may be prepared from compounds of formula (XV) by reaction with a halogenating agent such as N-bromo succinimide or 1,3-dibromo-5,5-dimethylhydantoin in the presence of a catalyst such as AIBN or benzoyl peroxide in a solvent such as dichloroethane or carbon tetrachloride using activation by light or heat at a temperature of from room temperature to reflux. Alternatively, compounds of formula (XVI) may be obtained from compounds of formula (XV) in a two step procedure by first formation of the pyridine N-oxide using an oxidizing agent such as 3-chloro-peroxy benzoic acid in a solvent such as DCM at a temperature of about room temperature. The intermediate N-oxides may be converted to halomethyl pyridines of formula (XVI) by reaction with a chlorinating agent such as phosphorous oxychloride. Compounds of formula (XVII) may be prepared from compounds of formula (XVI) by reaction with a protected form of ammonia such as potassium phthalimide or sodium diformyl imide in a solvent such as DMF at a temperature of from -5°C to 50°C. When R'''= H and R''''= C(=O)H compounds of formula (XVII) maybe converted to formyl amino nicotinic esters of formula (XVIII) by treatment with an acid such as formic acid or hydrochloric acid in a solvent such as methanol at a temperature of from room temperature to reflux. Compounds of formula (XVIII) may be cyclised to imidazopyridines of formula (XIX) by reaction with a phosphorous oxyhalide such as phosphorous oxychloride in a solvent such as toluene at a temperature of from 50°C to reflux. Alternatively, the cyclisation maybe effected using an acid such as formic acid or acetic acid, neat, at a temperature of from 25°C to reflux. Imidazopyridine-5-anilino esters of formula (XX) may be prepared from halides of formula (XIX) by reaction with an aniline (incorporating appropriate substituents R1), in the presence of a base such as lithium bis(trimethylsilyl)amide in a solvent such as THF at a temperature of from -78°C to room temperature. Alternatively, compounds of formula (XX) may be prepared from compounds of formula (XIX) by reaction with an aniline (incorporating appropriate substituents R1), in the presence of a catalyst such as tris(dibenzylideneacetone)dipalladium (0), a base such as potassium phosphate, a ligand such as 2-dicyclohexylphosphino-2',6'-(diisopropoxy)biphenyl, in a suitable solvent such as toluene, at a temperature of from room temperature to the reflux temperature of the solvent, or under microwave irradiation at a temperature of from 70°C to 150°C. Acids of formula (XXI) may be prepared from esters of formula (XX) using the methods described for the conversion of compounds of formula (VIII) to compounds of formula (IX) in Scheme 1. Alternatively, acids of formula (XXI) may be prepared from compounds of formula (XIX) first by saponification using the methods described for the conversion of compounds of formula (VIII) to compounds of formula (IX) followed by treatment with an aniline (incorporating appropriate substituents R1), in the presence of a base such as lithium (bistrimethylsilyl)amide in a solvent such as THF at a temperature of from -78°C to room temperature.

[0093] Anilino acids of formula (XXI) may be converted to compounds of formula (X) using the methods described for the conversion of compounds of formula (IX) to compounds of formula (X) in Scheme 1. In addition, esters of formula (XX) may be converted to compounds of formula (X) using the methods described for the conversion of compounds of formula (VIII) to compounds of formula (X) in Scheme 1.

[0094] Compounds of formula (XVI) and (XVII) may be prepared according to Scheme 3.

Scheme 3

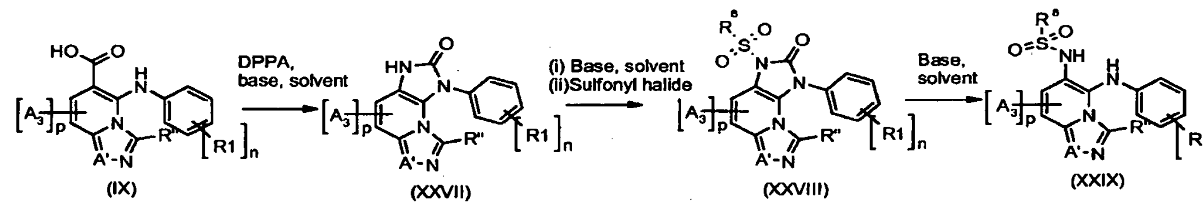


R'= Me, Et, lower alkyl
R= Cl, Br, (Formula (XVI) X= Cl or Br)
R= N_3, NH_2 (Formula (XVII) R'''=R''''= N2 or H)

[0095] Compounds of formula (XXIII) may be prepared from compounds of formula (XXII). Compounds of formula (XXII) are first esterified by formation of the bis-acid chloride using oxalyl chloride with catalytic DMF, in a solvent such as DCM, at a temperature of about room temperature followed by quench with an alcohol such as methanol. The resultant bis-ester intermediate may then be oxidized to compounds of formula (XXIII) by reaction with an oxidizing agent such as meta-chloro peroxybenzoic acid in a solvent such as DCM at a temperature of from 0°C to room temperature. Compounds of formula (XXV) may be prepared from compounds of formula (XXIV) by reduction with a metal hydride such as sodium borohydride in the presence of an additive such as calcium chloride, in a solvent such as ethanol, at a temperature of from 0°C to room temperature. Compounds of formula (XXV) may be converted to compounds of formula (XXVI) where R= Cl by halogenation using a sulfonyl chloride such as thionyl chloride in a solvent such as dichloromethane, at a temperature of from -5°C to room temperature. Compounds of formula (XXVI) where R= N_3 may be obtained from compounds of formula (XXV) by reaction with an azide such as diphenyl phosphoryl azide, in the presence of a diazocarboxylate such as diisopropyl azodicarboxylate, in the presence of a base such as triethylamine, in a solvent such as THF at a temperature of about room temperature. Compounds of formula (XXVI) where R= N_3 may be converted to compounds of formula (XXVI) where R= NH_2 by treatment with a reducing agent such as triphenyl phosphine in a solvent such as THF at a temperature of from room temperature to reflux.

[0096] Compounds of formula (I) where Y is R^8SO_2NH- may be prepared according to Scheme 4.

Scheme 4

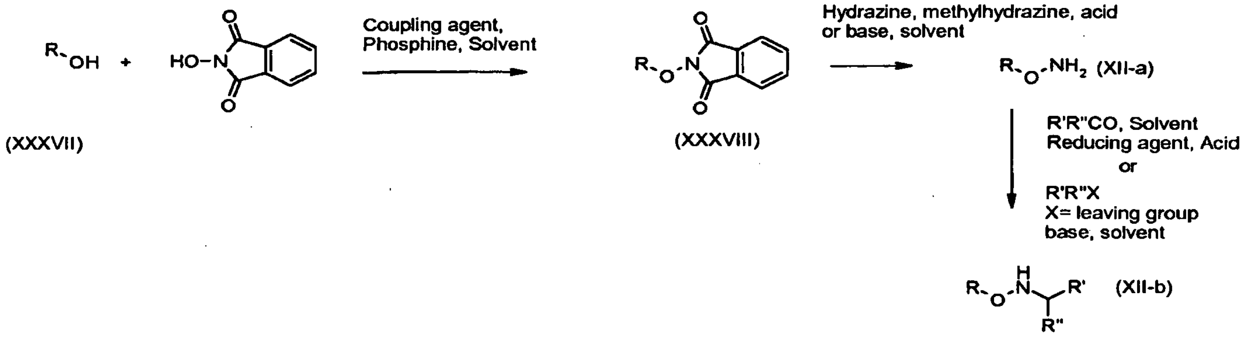


R''= H, methyl, ethyl or lower alkyl, CF_3
R1= appropriate substituent n= 0-4
A'= CH or N
A_3= halogen or other appropriate substituent
p= 0, 1 or 2

[0097] Compounds of formula (XXVII) may be prepared from compounds of formula (IX) by treatment with diphenylphosphoryl azide in a solvent such as toluene, in the presence of a base such as triethylamine. Compounds of formula (XXVIII) may be prepared from compounds of formula (XXVII) by treatment with a base such as sodium hydride, in a solvent such as DMF, followed by reaction with a sulfonyl chloride (appropriately substituted). Compounds of formula (XXIX) may be prepared from compounds of formula (XXVIII) by deprotection using a base such as sodium hydroxide, in a solvent such as DMF, at a temperature of from 50°C to 150°C.

[0098] Hydroxylamines of formula (XII) may be prepared using methods described in the literature or the synthetic route outlined in Scheme 5.

Scheme 5

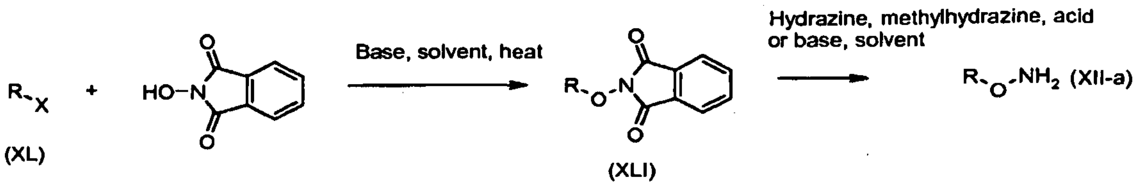


[0099] Primary or secondary alcohols of general formula (XXXVII) may be prepared using methods described in the literature. The alcohols may be reacted with N-hydroxy phthalimide using a phosphine and coupling reagent such as diethyl azodicarboxylate to provide compounds of general formula (XXXVIII). Compounds of general formula (XXXVIII) may be deprotected using hydrazine, methyl hydrazine, an acid such as hydrochloric acid or a base such as aqueous ammonia to provide hydroxylamines of general formula (XII-a).

[0100] Compounds of formula (XII-a) may be further modified by reductive amination with aldehydes or ketones using a reducing agent such as sodium triacetoxy borohydride, sodium cyanoborohydride, or borane-pyridine in a solvent such as dichloroethane at a temperature of from ambient temperature to reflux to provide hydroxylamines of general formula (XII-b). In addition, compounds of formula (XII-a) may be further modified by alkylation with an alkyl halide in the presence of a base such as triethylamine, in a solvent such as dichloromethane, to provide hydroxylamines of general formula (XII-b).

[0101] Alternatively, hydroxylamines of formula (XII-a) may be prepared according to Scheme 6.

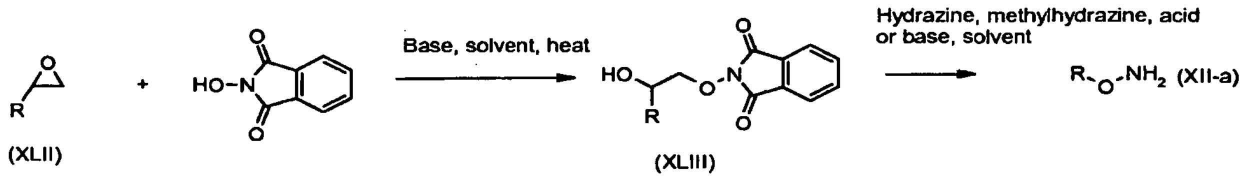
Scheme 6



[0102] Alkyl halides of formula (XL) may be reacted with N-hydroxy phthalimide in the presence of a base such as potassium carbonate in a solvent such as dimethyl sulfoxide at a temperature of from 10°C to 50°C. Compounds of formula (XLI) may be converted to compounds of formula (XII) using the methods described for the conversion of compounds of formula (XXXVIII) to compounds of formula (XII) in Scheme 5.

[0103] Alternatively, compounds of formula (XII-a) may be prepared according to Scheme 7.

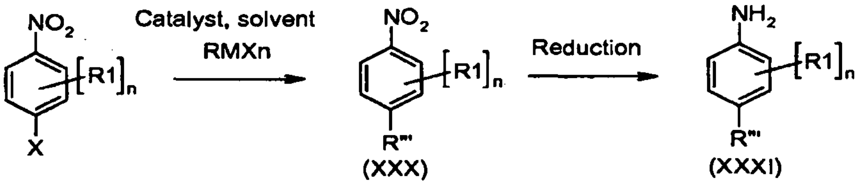
Scheme 7



[0104] Compounds of formula (XLII) may be reacted with N-hydroxy phthalimide in the presence of a catalytic amount of a base such as DIPEA and a co-catalyst such as tetrabutyl ammonium bromide in a solvent such as toluene at a temperature of form 50°C to reflux. Compounds of formula (XLIII) may be converted to compounds of formula (XII) using the methods described for the conversion of compounds of formula (XXXVIII) to compounds of formula (XII) in Scheme 5.

[0105] Anilines of general formula (XXXI) used in condensations and cross-coupling reactions described above may be prepared by using methods described in the literature or according to Scheme 8.

Scheme 8

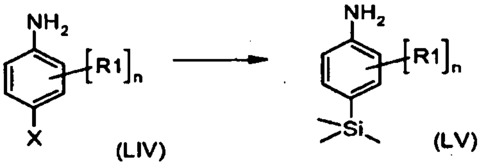


Where R1 is an optional substituent group,
n= 0-4
M= Metal
X= halogen
R'''= alkyl, cycloalkyl, vinyl, $SiMe_3$

[0106] Substituted 1-chloro-4-nitro benzene may be reacted with a metal R'''MXn, such as cyclopropyl boronic acid or hexamethyldisilazane, in a solvent such as xylene, using a catalyst such as tetrakis(triphenylphosphine)palladium, at a temperature of from room temperature to reflux to give compounds of formula (XXX). The nitro group may be reduced using methods described in the literature such as reaction under an atmosphere of hydrogen, at a pressure of from 1 to 5 atmospheres, in the presence of a catalyst such as palladium on carbon, and in a solvent such as ethanol or ethyl acetate, at room temperature to give compounds of formula (XXXI).

[0107] Alternatively, anilines of formula (LV) may be prepared according to Scheme 9.

Scheme 9



X= Br, I

[0108] 4-Bromo or iodo anilines of formula (LIV) may be reacted with at least 2 equivalents of a strong organometallic base such as n-butyllithium in a solvent such as THF at a temperature of from -100°C to -20°C followed by quench of the intermediate aryl lithium species with an electrophile such as trimethyl silyl chloride to give compounds of formula (LV).

[0109] It will be appreciated that where appropriate functional groups exist, compounds of formula (I) or any intermediates used in their preparation may be further derivatised by one or more standard synthetic methods employing substitution, oxidation, reduction, or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, sulfonylation, halogenation, nitration, formylation and coupling procedures.

[0110] For example, aryl bromide or chloride groups may be converted to aryl iodides using a Finkelstein reaction employing an iodide source such as sodium iodide, a catalyst such as copper iodide and a ligand such as trans-N,N'-dimethyl-1,2-cyclohexane diamine in a solvent such as 1,4-dioxane and heating the reaction mixture at reflux temperature. Aryl trialkylsilanes may be converted to aryl iodides by treating the silane with an iodide source such as iodine monochloride in a solvent such as dichloromethane with or without Lewis acid such as silver tetrafluoroborate at a temperature from -40°C to reflux.

[0111] In a further example primary amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde or a ketone and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, for example 1,2-dichloroethane, or an alcohol such as ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature. Secondary amine (-NH-) groups may be similarly alkylated employing an aldehyde.

[0112] In a further example, primary amine or secondary amine groups may be converted into amide groups (-NHCOR' or -NRCOR') by acylation. Acylation may be achieved by reaction with an appropriate acid chloride in the presence of a base, such as triethylamine, in a suitable solvent, such as dichloromethane, or by reaction with an appropriate carboxylic acid in the presence of a suitable coupling agent such HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) in a suitable solvent such as dichloromethane. Similarly, amine groups may be converted into sulfonamide groups ($-NHSO_2R'$ or $-NR''SO_2R'$) by reaction with an appropriate sulfonyl chloride in the presence of a suitable base, such as triethylamine, in a suitable solvent such as dichloromethane. Primary or secondary amine groups can be converted into urea groups (-NHCONR'R" or -NRCONR'R") by reaction with an appropriate isocyanate in the presence of a suitable base such as triethylamine, in a suitable solvent, such as dichloromethane.

[0113] An amine ($-NH_2$) may be obtained by reduction of a nitro ($-NO_2$) group, for example by catalytic hydrogenation, using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethyl acetate or an alcohol e.g. methanol. Alternatively, the transformation may be carried out by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

[0114] In a further example, amine ($-CH_2NH_2$) groups may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney nickel, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a temperature from -78°C to the reflux temperature of the solvent.

[0115] In a further example, amine ($-NH_2$) groups may be obtained from carboxylic acid groups ($-CO_2H$) by conversion to the corresponding acyl azide ($-CON_3$), Curtius rearrangement and hydrolysis of the resultant isocyanate (-N=C=O).

[0116] Aldehyde groups (-CHO) may be converted to amine groups ($-CH_2NR'R"$)) by reductive amination employing an amine and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, for example dichloromethane, or an alcohol such as ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

[0117] In a further example, aldehyde groups may be converted into alkenyl groups (-CH=CHR') by the use of a Wittig or Wadsworth-Emmons reaction using an appropriate phosphorane or phosphonate under standard conditions known to those skilled in the art.

[0118] Aldehyde groups may be obtained by reduction of ester groups (such as - CO_2Et) or nitriles (-CN) using diisobutylaluminium hydride in a suitable solvent such as toluene. Alternatively, aldehyde groups may be obtained by the oxidation of alcohol groups using any suitable oxidising agent known to those skilled in the art.

[0119] Ester groups ($-CO_2R'$) may be converted into the corresponding acid group ($-CO_2H$) by acid- or base-catalused hydrolysis, depending on the nature of R. If R is t-butyi, acid-catalysed hydrolysis can be achieved for example by treatment with an organic acid such as trifluoroacetic acid in an aqueous solvent, or by treatment with an inorganic acid such as hydrochloric acid in an aqueous solvent.

[0120] Carboxylic acid groups ($-CO_2H$) may be converted into amides (CONHR' or - CONR'R") by reaction with an appropriate amine in the presence of a suitable coupling agent, such as HATU, in a suitable solvent such as dichloromethane.

[0121] In a further example, carboxylic acids may be homologated by one carbon (i.e $-CO_2H$ to $-CH_2CO_2H$) by conversion to the corresponding acid chloride (-COCl) followed by Arndt-Eistert synthesis.

[0122] In a further example, -OH groups may be generated from the corresponding ester (e.g. $-CO_2R'$), or aldehyde (-CHO) by reduction, using for example a complex metal hydride such as lithium aluminium hydride in diethyl ether or tetrahydrofuran, or sodium borohydride in a solvent such as methanol. Alternatively, an alcohol may be prepared by reduction of the corresponding acid ($-CO_2H$), using for example lithium aluminium hydride in a solvent such as tetrahydrofuran, or by using borane in a solvent such as tetrahydrofuran.

[0123] Alcohol groups may be converted into leaving groups, such as halogen atoms or sulfonyloxy groups such as an alkylsulfonyloxy, e.g. trifluoromethylsulfonyloxy or arylsulfonyloxy, e.g. p-toluenesulfonyloxy group using conditions known to those skilled in the art. For example, an alcohol may be reacted with thioyl chloride in a halogenated hydrocarbon (e.g. dichloromethane) to yield the corresponding chloride. A base (e.g. triethylamine) may also be used in the reaction.

[0124] In another example, alcohol, phenol or amide groups may be alkylated by coupling a phenol or amide with an alcohol in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl, or dimethylazodicarboxylate. Alternatively alkylation may be achieved by deprotonation using a suitable base e.g. sodium hydride followed by subsequent addition of an alkylating agent, such as an alkyl halide.

[0125] Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange by treatment with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran, and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using N,N-dimethylformamide as the electrophile. Aromatic halogen substituents may alternatively be subjected to metal (e.g. palladium or copper) catalysed reactions, to introduce, for example, acid, ester, cyano, amide, aryl, heteraryl, alkenyl, alkynyl, thio- or amino substituents. Suitable procedures which may be employed include those described by Heck, Suzuki, Stille, Buchwald or Hartwig.

[0126] Aromatic halogen substituents may also undergo nucleophilic displacement following reaction with an appropriate nucleophile such as an amine or an alcohol. Advantageously, such a reaction may be carried out at elevated temperature in the presence of microwave irradiation.

[0127] The compounds of the present invention are tested for their capacity to inhibit MEK activity and activation (primary assays) and for their biological effects on growing cells (secondary assays) as described below. The compounds of the present invention having IC_{50} of less than 5 μM (more preferably less than 0.1 μM, most preferably less than 0.01 μM) in the MEK activity assay of Example 1, IC_{50} of less than 5 μM (more preferably less than 1 μM, even more preferably less than 0.1 μM, most preferably less than 0.01 μM) in the MEK activation assay of Example 2, EC_{50} of less than 10 μM (more preferably less than 1 μM, even more preferably less than 0.5 μM, most preferably less than 0.1 μM) in the cell proliferation assay of Example 3, and/or EC_{50} of less than 10 μM (more preferably less than 1 μM, even more preferably less than 0.5 μM, most preferably less than 0.1 μM) in the ERK phosphorylation assay of Example 4, are useful as MEK inhibitors.

[0128] The present invention includes a composition (e.g., a pharmaceutical composition) comprising a compound of formula I (and/or solvates and/or salts thereof) and a carrier (a pharmaceutically acceptable carrier). The present invention also includes a composition (e.g., a pharmaceutical composition) comprising a compound of formula I (and/or solvates and/or salts thereof) and a carrier (a pharmaceutically acceptable carrier), further comprising a second chemotherapeutic and/or a second anti-inflammatory agent such as those described herein. The present compositions are useful for inhibiting abnormal cell growth or treating a hyperproliferative disorder in a mammal (e.g., human). The present compositions are also useful for treating inflammatory diseases in a mammal (e.g., human).

[0129] The present compounds (such as any one of the title compounds of EXAMPLES 5-25) and compositions are also useful for treating an autoimmune disease, destructive bone disorder, proliferative disorders, infectious disease, viral disease, fibrotic disease or neurodegenerative disease in a mammal (e.g., human). Examples of such diseases/disorders include, but are not limited to, diabetes and diabetic complications, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, idiopathic pulmonary fibrosis, rhinitis and atopic dermatitis, renal disease and renal failure, polycystic kidney disease, congestive heart failure, neurofibromatosis, organ transplant rejection, cachexia, stroke, septic shock, heart failure, organ transplant rejection, Alzheimer's disease, chronic or neuropathic pain, and viral infections such as HIV, hepatitis (B) virus (HBV), human papilloma virus (HPV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). Chronic pain, for purposes of the present invention includes, but is not limited to, idiopathic pain, and pain associated with chronic alcoholism, vitamin deficiency, uremia, hypothyroidism, inflammation, arthritis, and post-operative pain. Neuropathic pain is associated with numerous conditions which include, but are not limited to, inflammation, postoperative pain, phantom limb pain, burn pain, gout, trigeminal neuralgia, acute herpetic and postherpetic pain, causalgia, diabetic neuropathy, plexus avulsion, neuroma, vasculitis, viral infection, crush injury, constriction injury, tissue injury, limb amputation, arthritis pain, and nerve injury between the peripheral nervous system and the central nervous system.

[0130] The present compounds (such as any one of the title compounds of EXAMPLES 5-25) and compositions are also useful for treating pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) in a mammal (e.g., human).

[0131] The present compounds (such as any one of the title compounds of EXAMPLES 5-25) and compositions are also useful for the prevention of blastocyte implantation in a mammal (e.g., human).

[0132] The present invention includes compounds of the present invention for use in a method of inhibiting abnormal cell growth or treating a hyperproliferative disorder in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound as set out in the claims or a composition thereof. Also included in the present invention is compounds of the present invention for use in a method of treating an inflammatory disease in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound as set out in the claims (and/or solvates and/or salts thereof) or a composition thereof.

[0133] The present invention includes compounds of the present invention for use in a method of inhibiting abnormal cell growm or treating a hyperproliferative disorder in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound as set out in the claims and/or salts thereof) or a composition thereof, in combination with a second chemotherapeutic agent such as those described herein. The present invention also includes a method of treating an inflammatory disease in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compoun as set out in the claims or a composition thereof, in combination with a second anti-inflammatory agent such as those described herein.

[0134] The present invention includes compounds of the present invention for use in a method of treating an autoimmune disease, destructive bone disorder, proliferative disorders, infectious disease, viral disease, fibrotic disease or neurodegenerative disease in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound as set out in the claims or a composition thereof, and optionally further comprising a second therapeutic agent. Examples of such diseases/disorders include, but are not limited to, diabetes and diabetic complications, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, idiopathic pulmonary fibrosis, rhinitis and atopic dermatitis, renal disease and renal failure, polycystic kidney disease, congestive heart failure, neurofibromatosis, organ transplant rejection, cachexia, stroke, septic shock, heart failure, organ transplant rejection, Alzheimer's disease, chronic or neuropathic pain, and viral infections such as HIV, hepatitis (B) virus (HBV), human papilloma virus (HPV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV).

[0135] The present invention includes compounds of the present invention for use in a method of treating pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound as set out in the claims or a composition thereof, and optionally further comprising a second therapeutic agent.

[0136] The present invention includes compounds of the present invention for use in a method for preventing of blastocyte implantation in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound as set out in the claims or a composition thereof, and optionally further comprising a second therapeutic agent.

[0137] It is also believed that the compounds of the present invention can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal (e.g., human) to treatment with radiation which comprises administering to said mammal an amount of a compound as set out in the claims or a composition thereof, which amount is effective is sensitizing abnormal cells to treatment with radiation.

[0138] Administration of the compounds of the present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, inhalation and rectal administration.

[0139] The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, preferably about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses maybe employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

[0140] The active compound may be applied as a sole therapy or in combination with one or more chemotherapeutic or anti-inflammatory agents, for example those described herein. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of treatment.

[0141] The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

[0142] Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[0143] Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

[0144] Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Ester, Pa., 15.sup.th Edition (1975).

EXAMPLES

Abbreviations

[0145]

nBuLi	n-Butyllithium
$CDCl_3$	Deuterated chloroform

(continued)

CD_3OD	Deuterated methanol
CH_2Cl_2	Dichloromethane
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDCI	1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride
Et_3N	Triethylamine
Et_2O	Diethyl ether
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl	Hydrochloric acid
HMN	Diatomaceous earth
HOBt	1-Hydroxybenzotriazole
H_2SO_4	Sulfuric acid
ICl	Iodine monochloride
IMS	Industrial methylated spirits
LHMDS	Lithium bis(trimethylsilyl)amide
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
$NaHCO_3$	Sodium hydrogen carbonate
Na_2SO_4	Sodium sulfate
NBS	N-Bromosuccinimide
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Pd_2dba_3	Tris-(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Si-PPC	Pre-packed silica flash chromatography cartridge: Isolute® SPE, Biotage SNAP® or ISCO Redisep®
SCX-2	Isolute ® silica-based sorbent with a chemically bonded propylsulfonic acid functional group.
THF	Tetrahydrofuran

General Experimental Conditions

[0146] ^{1}H NMR spectra were recorded at ambient temperature using a Varian Unity Inova (400MHz) spectrometer with a triple resonance 5mm probe. Chemical shifts are expressed in ppm relative to tetramethylsilane. The following abbreviations have been used: br = broad signal, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

[0147] High Pressure Liquid Chromatography - Mass Spectrometry (LCMS) experiments to determine retention times (R_T) and associated mass ions were performed using one of the following methods.

[0148] Method A: Experiments performed on a Waters Micromass ZQ quadrupole mass spectrometer linked to a Hewlett Packard HP1100 LC system with diode array detector. This system uses a Higgins Clipeus 5micron C18 100 x 3.0mm column and a 1 ml / minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1 % formic acid (solvent B) for the first minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 14 minutes. The final solvent system was held constant for a further 5 minutes.

[0149] Method B: Experiments performed on a Waters Platform LC quadrupole mass spectrometer linked to a Hewlett Packard HP1100 LC system with diode array detector and 100 position autosampler using a Phenomenex Luna C18(2) 30 x 4.6mm column and a 2 ml / minute flow rate. The solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.50 minutes followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 0.50 minutes.

[0150] Method C: Experiments performed on a PE Sciex API 150 EX quadrupole mass spectrometer linked to a Shimadzu LC-10AD LC system with diode array detector and 225 position autosampler using a Kromasil C 18 50 x 4.6mm column and a 3 ml / minute flow rate. The solvent system was a gradient starting with 100% water with 0.05%

TFA (solvent A) and 0% acetonitrile with 0.0375% TFA (solvent B), ramping up to 10% solvent A and 90% solvent B over 4 minutes. The final solvent system was held constant for a further 0.50 minutes.

[0151] Method D: Experiments performed on an Agilent Technologies liquid chromatography mass spectrometer linked to an Agilent Technologies Series 1200 LC system with diode array detector using a Zorbax 1.8 micron SB-C18 30 x 2.1 mm column with a 1.5 ml / minute flow rate. Method D1: The initial solvent system was 95% water containing 0.05% trifluoroacetic acid (solvent A) and 5% acetonitrile containing 0.05% trifluoroacetic acid (solvent B), followed by a gradient up to 5% solvent A and 95% solvent B over 1.5 minutes. The final solvent system was held constant for a further 1 minute. Method D2: The initial solvent system was 95% water containing 0.05% trifluoroacetic acid (solvent A) and 5% acetonitrile containing 0.05% trifluoroacetic acid (solvent B), followed by a gradient up to 5% solvent A and 95% solvent B over 3.0 minutes. The final solvent system was held constant for a further 1 minute.

[0152] Method E: Experiments performed on an Agilent Technologies liquid chromatography mass spectrometer linked to an Agilent Technologies Series 1200 LC system with diode array detector using a Zorbax 1.8 micron SB-C18 30 x 2.1 mm column with a 0.6 ml / minute flow rate. Method E1. The initial solvent system was 95% water containing 0.05% trifluoroacetic acid (solvent A) and 5% acetonitrile containing 0.05% trifluoroacetic acid (solvent B), followed by a gradient up to 5% solvent A and 95% solvent B over 9.0 minutes. The final solvent system was held constant for a further 1 minute. Method E2: The initial solvent system was 95% water containing 0.05% trifluoroacetic acid (solvent A) and 5% acetonitrile containing 0.05% trifluoroacetic acid (solvent B), followed by a gradient up to 5% solvent A and 95% solvent B over 20.0 minutes. The final solvent system was held constant for a further 1 minute.

[0153] Microwave experiments were carried out using a Personal Chemistry Emrys Iniatiator™ or Optimizer™, which uses a single-mode resonator and dynamic field tuning, both of which give reproducibility and control. Temperature from 40-250°C can be achieved, and pressures of up to 20bar can be reached.

Some of the compounds in the following examples are provided by way of comparison with the claimed compounds.

EXAMPLE 1 MEK Assay (MEK activity assay)

[0154] Constitutively activated human mutant MEK1 expressed in insect cells is used as source of enzymatic activity at a final concentration in the kinase assay of 15nM.

[0155] The assay is carried out for 30 minutes in the presence of 50μM ATP using recombinant GST-ERK1 produced in *E. Coli* as substrate. Phosphorylation of the substrate is detected and quantified using HTRF reagents supplied by Cisbio. These consist of an anti-GST antibody conjugated to allophycocyanin (XL665) and an anti-phospho (Thr202/Tyr204) ERK antibody conjugated to europium-cryptate. These are used at a final concentration of 4μg/ml and 0.84μg/ml respectively. The anti-phospho antibody recognises ERK1 dually phosphorylated on Thr202 and Tyr204. When both antibodies are bound to ERK1 (i.e. when the substrate is phosphorylated), energy transfer from the cryptate to the allophycocyanin occurs following excitation at 340nm, resulting in fluorescence being emitted that is proportional to the amount of phosphorylated substrate produced. Fluorescence is detected using a multiwell fluorimeter.

[0156] Compounds are diluted in DMSO prior to addition to assay buffer and the final DMSO concentration in the assay is 1%.

[0157] The IC_{50} is defined as the concentration at which a given compound achieves 50% inhibition of control. IC_{50} values are calculated using the XLfit software package (version 2.0.5).

[0158] Title compounds of Examples 5-20 and 22-24 exhibited an IC_{50} of less than 0.5 μM in the assay described in Example 1. Some of these compounds exhibited an IC_{50} of less than 0.1 μM in the assay described in Example 1. Title compounds of Examples 21 and 25 exhibited an IC_{50} of less than 10 μM in the assay described in Example 1.

EXAMPLE 2 bRaf Assay (MEK activation assay)

[0159] Constitutively activated bRaf mutant expressed in insect cells is used as source of enzymatic activity.

[0160] The assay is carried out for 30 minutes in the presence of 200μM ATP using recombinant GST-MEK1 produced in *E. Coli* as substrate. Phosphorylation of the substrate is detected and quantified using HTRF, and reagents are supplied by Cisbio. These consist of an anti-GST antibody conjugated to allophycocyanin (XL665) and an anti-phospho (Ser217/Ser221) MEK antibody conjugated to europium-cryptate. The anti-phospho antibody recognises MEK dually phosphorylated on Ser217 and Ser221 or singly phosphorylated on Ser217. When both antibodies are bound to MEK (i.e. when the substrate is phosphorylated), energy transfer from the cryptate to the allophycocyanin occurs following excitation at 340nm, resulting in fluorescence being emitted that is proportional to the amount of phosphorylated substrate produced. Fluorescence is detected using a multi-well fluorimeter.

[0161] Compounds are diluted in DMSO prior to addition to assay buffer and the final DMSO concentration in the assay is 1%.

[0162] The IC_{50} is defined as the concentration at which a given compound achieves 50% inhibition of control. IC_{50} values are calculated using the XLfit software package (version 2.0.5).

EXAMPLE 3 Cell Proliferation Assay

[0163] Compounds are tested in a cell proliferation assay using the following cell lines:

HCT116	human colorectal carcinoma (ATCC)
A375	human malignant melanoma (ATCC)

[0164] Both cell lines are maintained in DMEM/F12 (1:1) media (Gibco) supplemented with 10% FCS at 37°C in a 5% CO_2 humidified incubator.

[0165] Cells are seeded in 96-well plates at 2,000 cells/well and after 24 hours they are exposed to different concentrations of compounds in 0.83% DMSO. Cells are grown for a further 72h, and an equal volume of CellTiter-Glo reagent (Promega) is added to each well. This lyses the cells and generates a luminescent signal proportional to the amount of ATP released (and therefore proportional to the number of cells in the well) that can be detected using a multi-well luminometer.

[0166] The EC_{50} is defined as the concentration at which a given compound achieves 50% inhibition of control. IC_{50} values are calculated using the XLfit software package (version 2.0.5).

[0167] In this assay, title compounds of Example 5-8, 11-13 and 18-20 exhibited an EC_{50} of less than 0.5 μM in both cell lines. Some of the title compounds of Examples 5-8, 11-13 and 18-20 exhibited an EC_{50} of less than 0.1 μM in both cell lines. Title compounds of Examples 9-10 and 14-17 exhibited an EC_{50} of less than 0.8 μM in the HCT116 cell line.

EXAMPLE 4 Phospho-ERK Cell-Based Assay

[0168] Compounds are tested in a cell-based phospho-ERK ELISA using the following cell lines:

HCT116	human colorectal carcinoma (ATCC)
A375	human malignant melanoma (ATCC)

[0169] Both cell lines are maintained in DMEM/F12 (1:1) media (Gibco) supplemented with 10% FCS at 37°C in a 5% CO_2 humidified incubator.

[0170] Cells are seeded in 96-well plates at 2,000 cells/well and after 24h they are exposed to different concentrations of compounds in 0.83% DMSO. Cells are grown for a further 2h or 24h, fixed with formaldehyde (2% final) and permeabilised with methanol. Following blocking with TBST-3% BSA, fixed cells are incubated with primary antibody (anti-phospho ERK from rabbit) over-night at 4°C. Cells are incubated with Propidium Iodide (DNA fluorescent dye) and detection of cellular p-ERK is performed using an anti-rabbit secondary antibody conjugated to the fluorescent Alexa Fluor 488 dye (Molecular probes). The fluorescence is analysed using the Acumen Explorer (TTP Labtech), a laser-scanning microplate cytometer, and the Alexa Fluor 488 signal is normalised to the PI signal (proportional to cell number).

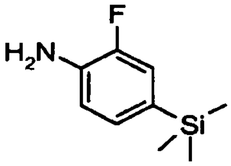
[0171] The EC_{50} is defined as the concentration at which a given compound achieves a signal half way between the baseline and the maximum response. EC_{50} values are calculated using the XLfit software package (version 2.0.5).

[0172] In this assay, title compounds of Examples 5-8, 11-12 and 18-20 exhibited an EC_{50} of less than 0.02 μM in both cell lines. Some of the title compounds of Examples 5-8, 11-12 and 18-20 exhibited an EC_{50} of less than 0.01 μM in both cell lines. Title compounds of Examples 9-10 and 13-17 exhibited an EC_{50} of less than 0.05 μM in the HCT116 cell line.

SYNTHESIS OF IMIDAZO[1,5-a]PYRIDINES

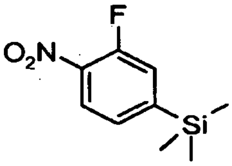
2-Fluoro-4-trimethylsilanyl-phenylamine

[0173]



Method A, step 1: (3-Fluoro-4-nitro-phenyl)-trimethylsilane

[0174]



[0175] 4-Chloro-2-fluoronitrobenzene (97.2 g, 0.55 mol) was dissolved in xylenes (208 ml) and hexamethyldisilane (306 g, 2.78 mol) was added. Argon was bubbled through the mixture for 20 min, then $Pd(PPh_3)_4$ (16.2 g, 14 mmol) was added and the mixture was heated under continuous flow of argon at 150°C for 1 hour. A balloon of argon was then fitted and the mixture was heated at 150°C for a further 60 hours. After cooling the mixture was diluted with diethyl ether and filtered through a pad of silica. The filter cake was washed with further diethyl ether, and the combined filtrates were concentrated *in vacuo.* Purification of the resultant residue by flash chromatography (SiO_2, 98:1:1 pentane:CH_2Cl_2:Et_2O eluent) gave the title compound as an orange oil (76.7 g). Impure chromatography fractions were combined and concentrated, and then subjected to vacuum distillation (b.p.110°C, 6 mbar) to give a further portion of the title compound as an orange oil (7.2 g, overall 83.9g, 71 %). ^1H NMR δ (DMSO-d_6): 0.30 (9 H, s), 7.56 (1 H, d, J = 8.02 Hz), 7.67 (1 H, dd, J = 11.49, 1.14 Hz), 8.10 (1 H, t, J = 7.66 Hz).

Method A, step 2: 2-Fluoro-4-trimethylsilanyl-phenylamine

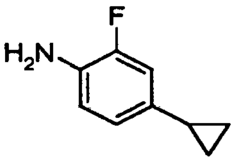
[0176] A slurry of 10% wt. palladium on carbon (4.0 g) in IMS (25 mL) was added to a solution of (3-fluoro-4-nitro-phenyl)-trimethylsilane (62.0 g, 0.29 mol) in IMS (250 mL) and the reaction mixture flushed with nitrogen five times then hydrogen three times. The reaction mixture was then stirred under 3 bar pressure of hydrogen at room temperature for 4 hours. The reaction mixture was then purged with nitrogen again before filtering through a pad of Celite ® with ethyl acetate washings. The filtrate was concentrated under reduced pressure to give the title compound as a light brown oil (53.0 g, quantitative). ^1H NMR ($CDCl_3$) 7.16-7.09 (1H, m), 7.10 (1 H, d, J = 7.75 Hz), 6.81 (1 H, t, J = 8.16 Hz), 3.78 (2 H, s), 0.26 (9 H, s).

Method B, step 2 : 2-Fluoro-4-trimethylsilanyl-phenylamine

[0177] To a solution of4-bromo-2-fluoro-phenylamine (114 g, 0.6 mol) in anhydrous THF (750 mL) at -78°C was added a 1.6M solution of nBuLi in hexanes (1500 mL, 2.4 mol) dropwise keeping the internal temperature below -60°C, under an inert atmosphere. The reaction mixture was treated dropwise with TMSCl (256 mL, 2.0 mol), keeping the internal temperature below -60°C. The reaction mixture was allowed to warm to 0°C over a 1 hour period and poured into ice-cold 2M HCl (ca. 1L). The mixture was vigorously stirred for 10 min, then the organic layer was separated, and washed with water and a saturated solution of potassium carbonate, dried (Na_2SO_4), filtered and concentrated to give the title compound as a light brown oil (89 g, 81%).

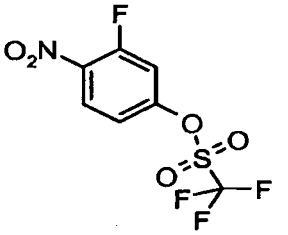
4-Cyclopropyl-2-fluoro-phenylamine

[0178]



Step 1: Trifluoro-methanesulfonic acid 3-fluoro-4-nitro-phenyl ester

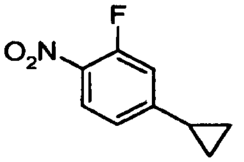
[0179]



[0180] To a solution of 3-fluoro-4-nitrophenol (12.5 g, 80 mmol) and trifluoromethane sulfonic anhydride (26.8 mL, 160 mmol) in DCM (300 mL) at 0°C was added triethylamine (44.6 mL, 320 mmol) dropwise. The reaction mixture was stirred at 0°C for 2 hours then allowed to warm to room temperature and stirred for 18 hours. The reaction was quenched by the addition of water and the mixture extracted with DCM. The organic layer was separated, washed with water and then dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0 to 40% ethyl acetate in cylcohexane) to give the title compound as a yellow oil (12.8g, 56% yield). ^1H NMR (DMSO-d_6, 400 MHz) 8.39 (1 H, t, J = 8.83 Hz), 8.12 (1 H, dd, J = 11.09, 2.65 Hz), 7.67 (1 H, ddd, J = 9.20, 2.62, 1.52 Hz).

Step 2: 4-Cyclopropyl-2-fluoro-1-nitro-benzene

[0181]



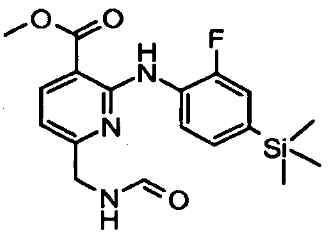
[0182] A stirred suspension of trifluoro-methanesulfonic acid 3-fluoro-4-nitro-phenyl ester (5.6 g, 19 mmol), cyclopropyl boronic acid (2.09 g, 23.3 mmol) Pd(dppf)Cl_2 (1.24 g, 1.5 mmol) and 2M aqueous cesium carbonate (30 mL, 60 mmol) in toluene (20 mL) was degassed before being heated at 90°C under an argon atmosphere for 2.5 hours. The reaction mixture was allowed to cool to room temperature before filtering through a pad of Celite ®, washing with ethyl acetate. The filtrate was washed (water, brine), and then dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0-30% ethyl acetate in pentane) to give the title compound as a yellow solid (2.79 g, 81%). ^1H NMR (DMSO-d_6, 400 MHz) 8.03 (1 H, t, J = 8.39 Hz), 7.28 (1 H, dd, J = 13.19, 1.91 Hz), 7.16 (1 H, dd, J = 8.61, 1.90 Hz), 2.14-2.05 (1 H, m), 1.21-1.05 (2 H, m), 0.92-0.82 (2 H, m).

Step 3: 4-Cyclopropyl-2-fluoro-phenylamine

[0183] A slurry of palladium on carbon (200 mg, 10% wt.) in IMS was added to a degassed solution of 4-cyclopropyl-2-fluoro-1-nitro-benzene (1.45 g, 8 mmol) in IMS (50 mL), the atmosphere was evacuated and back-filled with nitrogen then re-evacuated and back-filled with hydrogen. The reaction mixture was stirred under 1 atmosphere pressure of hydrogen at room temperature for 24 hours before filtering through a pad of Celite ® then washing with ethyl acetate. The filtrate was concentrated *in vacuo* to give the title compound as a pale purple residue (1.19 g, 98%). ^1H NMR ($CDCl_3$, 400 MHz) 6.72-6.63 (3 H, m), 3.56 (2 H, s), 1.83-1.75 (1 H, m), 0.93-0.82 (2 H, m), 0.59-0.54 (2 H, m).

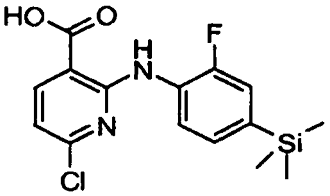
2-(2-Fluoro-4-trimethylsilanyl-phenylamino)-6-formylaminomethyl-nicotinic acid methyl ester

[0184]



Step 1: 6-Chloro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)nicotinic acid

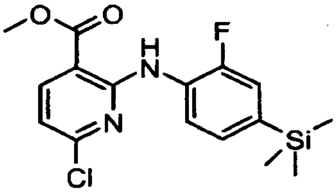
[0185]



[0186] To a cold (-78°C) solution of 2-fluoro-4-trimethylsilanyl-phenylamine (64.7 g, 353 mmol) in anhydrous THF (170 mL) was added a solution of LHMDS (555 mL, 1 M in hexanes, 555 mmol) dropwise over 45 minutes under a nitrogen atmosphere. After 2.5 hours at -78°C, a solution of 2,6-dichloro-nicotinic acid (33.8 g, 177 mmol) in anhydrous THF (100 mL) was added. The reaction mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature. After 18 hours stirring at room temperature the reaction was quenched with crushed ice and the pH adjusted to pH 1 by the addition of concentrated HCl (ca. 90 mL). The resultant solution was extracted with ethyl acetate and the organic layer washed with water followed by brine, dried (Na_2SO_4), filtered and *evaporated in vacuo.* The resultant residue was triturated three times successively with methanol and filtered to afford the title compound as a yellow solid (46.7 g, 78%). LCMS (method B): R_T = 4.83 min, $M+H^+$ = 339.

Step 2: 6-Chloro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid methyl ester

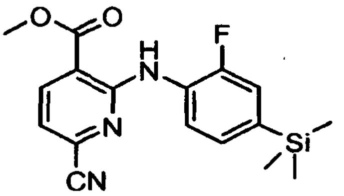
[0187]



[0188] To a suspension of 6-chloro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid (33.7 g, 99.5 mmol) in dichloromethane (500 mL) at 0°C was added DIPEA (17.1 mL, 99.5 mmol). The reaction mixture was stirred for 10 minutes, then DMF (2 mL) and oxalyl chloride (8.7 mL, 99.5 mmol) were added dropwise (CAUTION : EFFERVESCENCE). The reaction mixture was stirred at room temperature for 2 hours and then added dropwise to a solution of DIPEA (17.1 mL, 99.5 mmol) in MeOH (500 mL) at 0°C over a 45 minutes period. The reaction mixture was stirred at room temperature for 18 hours before being concentrated *in vacuo.* The resultant residue was dissolved in ethyl acetate and washed with a saturated aqueous solution of sodium hydrogen carbonate, followed by water, then brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to afford the title compound as a brown foam which was used without purification into the next step (36.4 g). LCMS (method B) R_T = 5.35 min, $M+H^+$ = 353.

Step 3: 6-Cyano-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid methyl ester

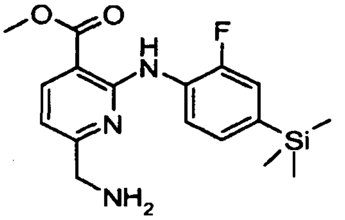
[0189]



[0190] A degassed suspension of 6-chloro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid methyl ester (4.8 g, 12.4 mmol), zinc cyanide (1.2 g, 10.2 mmol), and $Pd(PPh_3)_4$ (1.6 g, 1.36 mmol) in dimethylformamide (14 mL) was subjected to microwave irradiation at 190°C for 20 minutes. This procedure was repeated seven times and all the reaction mixtures were combined and *concentrated in vacuo.* The resultant residue was dissolved in ethyl acetate and washed with a saturated aqueous solution of sodium hydrogen carbonate. The aqueous layer was separated and extracted with ethyl acetate three times. The combined organic extracts were washed with water and then brine, dried (Na_2SO_4), filtered and evaporated *in vacuo.* The resultant residue was subjected to flash chromatography (silica, gradient 0% to 100%, diethyl ether in pentane) to afford the title compound as a yellow solid (18.2 g). LCMS (method B): R_T = 4.74 min, $M+H^+$ = 344.

Step 4: 6-Aminomethyl-2-(2-fluoro-4-trimethylsilanyl-phenylamino)nicotinic acid methyl ester

[0191]



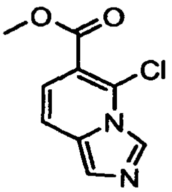
[0192] To a suspension of 6-cyano-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid methyl ester (13.1 g, 38.2 mmol) in methanol (285 mL) was added cobalt (II) chloride (18.2 g, 76.4 mmol). The reaction mixture was cooled to 0°C and sodium borohydride (14.5 g, 382 mmol) was added in small portions over 20 minutes (CAUTION : EFFERVESCENCE). The reaction mixture was stirred at 0°C for 1 hour. The reaction was quenched by the addition of concentrated hydrochloric acid (50 mL) and the mixture stirred at 0°C for 10 minutes and at room temperature for 45 minutes. Diethylenetriamine (9 mL) was then added and the mixture stirred for a further 15 minutes. The reaction mixture was filtered to remove a white solid, which was washed with dichloromethane. The filtrate was concentrated *in vacuo* and the resultant residue was dissolved in ethyl acetate and washed with a saturated solution of sodium hydrogen carbonate, followed by water then brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a brown solid (13.2 g, 100%). LCMS (method B): R_T = 2.82 min, $M+H^+$ = 348.

Step 5: 2-(2-Fluoro-4-trimethylsilanyl-phenylamino)-6-formylaminomethyl-nicotinic acid methyl ester

[0193] A solution of 6-aminomethyl-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid methyl ester (13.2 g, 38.2 mmol) in formic acid (200 mL) and acetic anhydride (40 mL) was stirred at ambient temperature for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue azeotroped with toluene. The resultant residue was dissolved in dichloromethane and washed with a saturated aqueous solution of sodium hydrogen carbonate, followed by brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a yellow solid (12.7 g, 89%). LCMS (method B): R_T = 4.17 min, $M+H^+$ = 376.

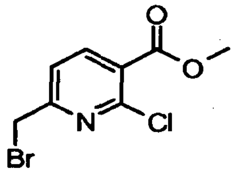
5-Chloro-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester

[0194]



Step 1, Method A: 6-Bromomethyl-2-chloronicotinic acid methyl ester

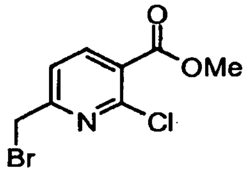
[0195]



[0196] To a solution of 2-chloro-6-methylnicotinic acid methyl ester (100 g, 0.54 mol) in DCE (1.0 L) was added recrystallised N-bromosuccinimide (124.7 g, 0.70 mol) and benzoylperoxide (13.1 g, 0.05 mol). The reaction mixture was heated at 70°C for 16 hours, during which the reagents dissolved to give a dark red solution. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (200 mL) causing the red colour to fade to yellow. The aqueous layer was extracted with DCM (2 x 100 mL). The combined organic fractions were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product (<138 g, <0.54 mol) as a yellow oil containing approximately 40% desired product. ^{1}H NMR ($CDCl_3$, 400MHz) 8.18 (1H, d, J = 8.0 Hz), 7.48 (1H, d, J = 7.9 Hz), 4.51 (2H, s), 3.94 (3H, s).

Step 1, Method B: Alternative method 6-Bromomethyl-2-chloronicotinic acid methyl ester

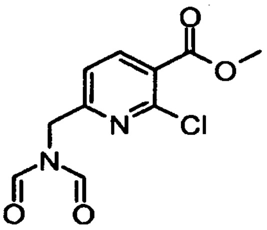
[0197]



[0198] To a mechanically stirred solution of 2-chloro-6-methylnicotinic acid methyl ester (147 g, 0.79 mol) in DCE (1.5 L) was added 1,3- dibromo-5,5-dimethylhydantoin (181.8 g, 0.635 mol) and AIBN (6.35 g, 0.04 mol). The reaction mixture was heated at 65°C for 72 hours, during which the reagents dissolved to give a dark red/ brown solution. The reaction mixture was cooled and diluted with saturated aqueous sodium hydrogen carbonate solution (1 L) causing the red colour to fade to yellow. The layers were separated, and the aqueous layer was extracted with DCM (2 × 750 mL). The combined organic fractions were washed with water (1 L), sat. saline (1 L), dried ($MgSO_4$) and *concentrated in vacuo.* The resultant yellow oil (235 g), containing approximately 46% desired product, was used crude in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400MHz) 8.18 (1H, d, J = 8.0 Hz), 7.48 (1H, d, J = 7.9 Hz), 4.51 (2H, s), 3.94 (3H, s).

Step 2, Method A: 2-Chloro-6-diformylaminomethylnicotinic acid methyl ester

[0199]



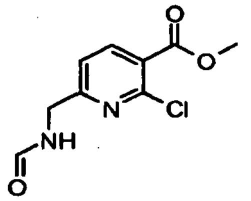
[0200] To a solution of crude 6-bromomethyl-2-chloronicotinic acid methyl ester (<138 g, <0.54 mol) in DMF (400 mL) was added sodium diformamide (56.3 g, 0.59 mol) and the reaction mixture stirred at room temperature for 16 hours. The reaction mixture rapidly darkened and a small exotherm was observed. The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate (200 mL). The resultant solution was washed with water (400 mL) and the aqueous layer extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and *concentrated in vacuo.* The resultant residue was dry-loaded onto silica (150 g) and the residue subjected to flash chromatography (SiO_2 400 g, 40% ethyl acetate in cyclohexane) to yield the title compound as a yellow solid (46 g, 33% over two steps). ^1H NMR ($CDCl_3$, 400MHz) 8.46 (2H, br s), 7.56 (1H, d, J = 7.7 Hz), 6.66 (1H, d, J = 7.9 Hz), 4.39 (2H, br s), 3.36 (3H, s).

Step 2, Method B: 2-Chloro-6-diformylaminomethylnicotinic acid methyl ester

[0201] To a solution of crude 6-bromomethyl-2-chloronicotinic acid methyl ester (235 g) in DMF (500 mL) was added sodium diformamide (82 g, 0.878 mol) portion wise, maintaining the temperature below 30°C, and the reaction mixture stirred at room temperature for 16 hours (*N.B.* the reaction mixture rapidly darkened and a small exotherm was observed). The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate (400 mL). The resultant solution was washed with water (2 x 400 mL) and the aqueous layer extracted with ethyl acetate (2 x 300 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The resultant residue was dry-loaded onto silica (200 g) and the residue subjected to flash chromatography (SiO_2 300 g, 10-30% ethyl acetate in cyclohexane) to yield the title compound as a yellow solid (90.2 g, 44% over two steps). ^1H NMR ($CDCl_3$, 400MHz) 8.46 (2H, br s), 7.56 (1H, d, J = 7.7 Hz), 6.66 (1H, d, J = 7.9 Hz), 4.39 (2H, br s), 3.36 (3H, s).

Step 3, Metohd A: 2-Chloro-6-formylaminomethylnicotinic acid methyl ester

[0202]



[0203] To a solution of 2-chloro-6-diformylaminomethylnicotinic acid methyl ester (53.0 g, 0.21 mol) in methanol (300 mL) was added water (3.72 mL, 0.21 mol) and formic acid (15.6 mL, 0.42 mol) before the reaction mixture was heated at reflux for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate (200 mL). The resultant solution was washed with water (200 mL) and the aqueous layer extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as an orange oil which solidified on standing (42.6 g, 90%). ^1H NMR ($CDCl_3$, 400MHz) 8.34 (1H, s), 8.17 (1H, d, J = 8.0 Hz), 7.31 (1H, d, J = 7.8 Hz), 6.63 (1H, br s), 4.63 (2H, d, J = 5.6 Hz), 3.96 (3H, s).

Step 3, Method B: 2-Chloro-6-formylaminomethylnicotinic acid methyl ester

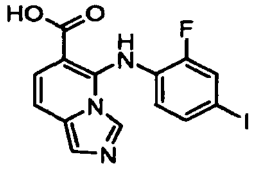
[0204] To a solution of 2-chloro-6-diformylaminomethylnicotinic acid methyl ester (90.2 g, 0.352 mol) in methanol (530 mL) was added water (8 mL, 0.44 mol) and formic acid (27.6 mL, 0.73 mol) before the reaction mixture was heated at gentle reflux for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate (400 mL). The resultant solution was washed with water (400 mL) and the aqueous layer extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$) and *concentrated in* *vacuo* to yield the title compound as an orange oil which solidified on standing (79.78g, 99%). ^{1}H NMR (CDCl$_3$, 400MHz) 8.34 (1H, s), 8.17 (1H, d, J = 8.0 Hz), 7.31 (1H, d, J = 7.8 Hz), 6.63 (1H, br s), 4.63 (2H, d, J = 5.6 Hz), 3.96 (3H, s).

Step 4: 5-Chloroimidazo[1,5-a]pyridine-6-carboxylic acid methyl ester

[0205] To a suspension of 2-chloro-6-formylaminomethylnicotinic acid methyl ester (42.6 g, 0.19 mol) in toluene (400 mL) was added phosphorous (V) oxychloride (18.2 mL, 0.20 mol) and the reaction mixture heated at 65°C for 1.5 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (200 mL) before treating with sodium hydroxide solution (2 M) to adjust pH~8. The layers were separated and the aqueous layer extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried (MgSO$_4$) then charcoal (~5 g) was added and the solution mixed for 5 minutes before being filtered and concentrated *in vacuo* to yield the title compound as a tan solid (34.4 g, 88%) ^{1}H NMR (CDCl$_3$, 400MHz) 8.52 (1H, s), 7.57 (1H, s), 7.45 (1H, d, J = 9.3 Hz), 7.25 (1H, d, J = 9.1 Hz), 3.97 (3H, s).

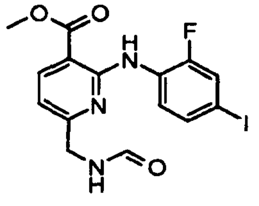
5-(2-Fluoro-4-iodophenylamino)-imidazo[1.5-a]pyridine-6-carboxylic acid

[0206]



Step 1: 2-(2-Fluoro-4-iodophenylamino)-6-formylaminomethylnicotinic acid methyl ester

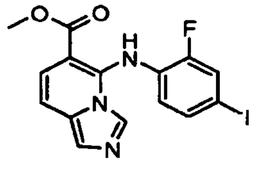
[0207]



[0208] To a solution of 2-(2-fluoro-4-trimethylsilanylphenylamino)-6-formylamino methyl-nicotinic acid methyl ester (10.3 g, 27.4 mmol) in DCM (275 mL) at 0°C was added dropwise iodine monochloride as a solution in DCM (54.9 mL, 1M, 54.9 mmol). The reaction mixture was stirred at 0°C for 1 hour. The reaction mixture was washed with aqueous sodium metabisulfite (100 mL, 0.5 M) and the aqueous layer extracted twice with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give the title compound as an orange gum (11.6 g, 100%). LCMS (Method B): R$_T$ = 3.72 min, M+H$^+$ = 430.

Step 2: 5-(2-Fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester

[0209]



[0210] To a suspension of 2-(2-fluoro-4-iodophenylamino)-6-formylaminomethylnicotinic acid methyl ester (11.6 g, 27.4 mmol) in toluene (160 mL) was added phosphorous (V) oxychloride (5.1 mL, 54.8 mmol) and the reaction mixture heated at 95°C for 1 hour. The reaction mixture was concentrated *in vacuo* and the resultant residue poured onto ice.

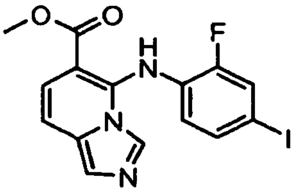
The mixture was washed with aqueous saturated sodium hydrogen carbonate solution (40 mL) and the aqueous layer extracted twice with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 0-70% ethyl acetate in DCM) to yield the title compound as a brown oil (5.6 g, 50%). LCMS (Method B): R_T = 3.62 min, $M+H^+$ = 412.

Step 3: 5-(2-Fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid

[0211] To a solution of 5-(2-fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (5.6 g, 13.6 mmol) in IMS (50 mL) was added aqueous sodium hydroxide (27.2 mL, 1M, 27.2 mmol) and the reaction mixture stirred at 65°C for 2 hours. The reaction mixture was concentrated *in vacuo* to remove the IMS. The resultant solution was acidified to pH ~5 by addition of aqueous hydrochloric acid (1M) causing a precipitate to form. The product was collected by filtration and dried under vacuum at 45°C to yield the title compound as a beige solid (5.4 g, 100%). LCMS (Method B): R_T = 2.79 min, $M+H^+$ = 398.

5-(2-Fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester, Method A

[0212]

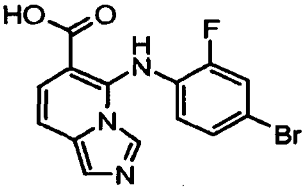


[0213] To a solution of lithium bis(trimethylsilyl) amide (9.98 mL, 1M solution, 9.98 mmol) in THF (20 mL) under nitrogen at -70°C was added dropwise, over 15 minutes, a solution of 2-fluoro-4-iodo aniline (1.01 g, 4.28 mmol) and 5-chloro-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (1.0 g, 4.75 mmol) in THF (20 mL) giving a bright red solution. After stirring for 30 minutes at -78°C the reaction mixture was allowed to warm and then quenched with saturated aqueous ammonium chloride (200 mL). The mixture was extracted twice with ethyl acetate, before the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0-40% ethyl acetate in cyclohexane) to yield the title compound as a yellow solid (1.15 g, 65%). LCMS (Method B): R_T = 3.54 min, $M+H^+$ = 412.

5-(2-Fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester, Method B

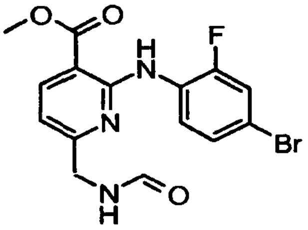
[0214] To a stirred suspension 2-fluoro-4-iodo aniline (53.95 g, 0.256 mol) and 5-chloro-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (62.0 g, 0.253 mol) in THF (500 mL) under nitrogen at -78°C, a solution of lithium bis(trimethylsilyl) amide (544 mL, 1M solution, 0.544 mol) was added dropwise over 1 hr, maintaining the temperature below - 65°C, giving a red/ brown solution. After stirring for 30 minutes at -78°C the reaction mixture was allowed to warm to -30°C and then quenched with addition water (100 mL). The solvent was removed *in vacuo,* before diluting with water (500ml) and the mixture was extracted with 2-methyltetrahydrofuran (2 x 500mL). The combined organic extracts were washed with water, then brine, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue was triturated tert-butyl methyl ether (600mL) to yield product as yellow/brown solid (87.2g 83%). LCMS (Method B): R_T = 3.54 min, $[M+H]^+$ = 412.

[0215] 5-(4-Bromo-2-fluorophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid



Step 1: 2-(4-Bromo-2-fluorophenylamino)-6-formylaminomethylnicotinic acid methyl ester

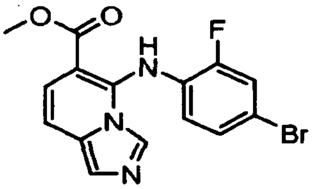
[0216]



[0217] To a solution of 2-(2-fluoro-4-trimethylsilanylphenylamino)-6-formylamino methyl-nicotinic acid methyl ester (11.6 g, 30.9 mmol) in DCM (300 mL) at -30°C was added N-bromo succinimide (5.56 g, 30.9 mmol) portionwise. The reaction mixture was stirred at - 30°C for 30 minutes. The reaction mixture was concentrated *in vacuo* and the residue partitioned between saturated aqueous sodium hydrogen carbonate and ethyl acetate. The organic layer was separated and washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound as an orange gum (11.8 g, 100%). LCMS (Method B): R_T = 3.67 min, $M+H^+$ = 382/384.

Step 2: 5-(4-Bromo-2-fluorophenylamino)-imidazo[1.5-a]pyridine-6-carboxylic acid methyl ester

[0218]



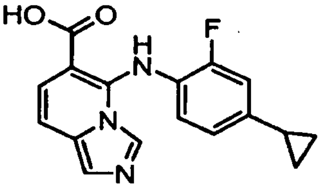
[0219] To a solution of 2-(4-Bromo-2-fluorophenylamino)-6-formylaminomethylnicotinic acid methyl ester (11.8 g, 30.9 mmol) in toluene (550 mL) was added phosphorous (V) oxychloride (3.16 mL, 34 mmol) and the reaction mixture heated at 95°C for 1 hour. The reaction mixture was concentrated *in vacuo* and treated with aqueous saturated sodium hydrogen carbonate solution then extracted twice with ethyl acetate. The combined organic fractions were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0-30% ethyl acetate in DCM) to yield the title compound as a brown oil (5.4 g, 49%). LCMS (Method B): R_T = 3.56 min, $M+H^+$ = 364/366.

Step 3: 5-(4-Bromo-2-fluorophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid

[0220] To a solution of 5-(4-Bromo-2-fluorophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (5.4 g, 15 mmol) in IMS (110 mL) was added aqueous sodium hydroxide (30 mL, 1M, 30 mmol) and the reaction mixture stirred at 65°C for 1.5 hours. The reaction mixture was concentrated *in vacuo* to ~50 mL volume and the resultant solution was acidified to pH ~2 by addition of aqueous hydrochloric acid (1M) causing a precipitate to form. The precipitate was collected by filtration and dried under vacuum at 35°C to yield the title compound as a dark tan solid (4.48 g, 85%). LCMS (Method B): R_T = 2.81 min, $M+H^+$ = 350/352.

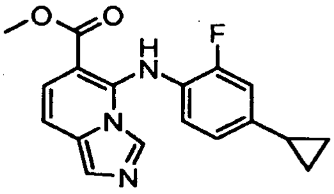
5-(2-Fluoro-4-cyclopropylphenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid

[0221]



Step 1: 5-(2-Fluoro-4-cyclopropylphenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester

[0222]



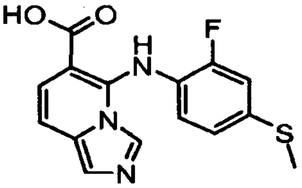
[0223] To a solution of 2-fluoro-4-cyclopropyl aniline (395 mg, 2.61 mmol) and 5-chloro-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (500 mg, 2.37 mmol) in THF under nitrogen at -70°C (20 mL) was added lithium bis(trimethylsilyl) amide (4.98 mL, 1M solution, 4.98 mmol) dropwise. After stirring for 1 hour at -70°C the reaction mixture was allowed to warm and then quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate (150 mL), the organic extract dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0-50% ethyl acetate in cyclohexane) to yield the title compound (573 mg, 60%). LCMS (Method B): R_T = 3.60 min, $M+H^+$ = 326.

Step 2: 5-(2-Fluoro-4-cyclopropylphenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid

[0224] To a solution of 5-(2-fluoro-4-cyclopropylphenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (573 mg, 1.73 mmol) in methanol (20 mL) was added aqueous sodium hydroxide (10 mL, 1M, 10 mmol) and the reaction mixture stirred at 70°C for 30 minutes. The reaction mixture was concentrated *in vacuo* to ~20 mL volume and the resultant solution diluted with water (20 mL) and filtered. The filtrate was acidified to pH ~1 by addition of aqueous hydrochloric acid (1M) causing a precipitate to form. The precipitate was collected by filtration and dried under vacuum at 45°C to yield the title compound as a dark tan solid (476 mg, 87%). LCMS (Method B): R_T = 2.81 min, $M+H^+$ = 318.

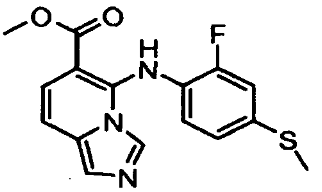
5-(2-Fluoro-4-methansulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid, Method A

[0225]



Step 1: 5-(2-Fluoro-4-methylsulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester

[0226]



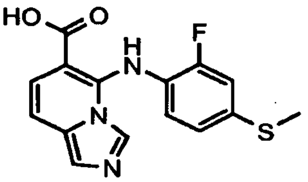
[0227] To a solution of 2-fluoro-4-methanesulfanyl phenyl amine (410 mg, 2.61 mmol) and 5-chloro-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (500 mg, 2.37 mmol) in THF under nitrogen at -70°C (20 mL) was added lithium bis(trimethylsilyl) amide (4.98 mL, 1M solution, 4.98 mmol) dropwise. After stirring for 30 minutes at -70°C the reaction mixture was allowed to warm and then quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate (150 mL), the organic extract washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0-50% ethyl acetate in cyclohexane) to yield the title compound (471 mg, 73%). LCMS (Method B): R_T = 3.39 min, $M+H^+$ = 332.

Step 2: 5-(2-Fluoro-4-methansulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid

[0228] To a solution of 5-(2-fluoro-4-methanesulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (471 mg, 1.45 mmol) in methanol (20 mL) was added aqueous sodium hydroxide (10 mL, 1M, 10 mmol) and the reaction mixture stirred at 70°C for 30 minutes. The reaction mixture was concentrated *in vacuo* to ~20 mL volume and the resultant solution diluted with water (20 mL) before being acidified to pH ~1 by addition of aqueous hydrochloric acid (1M) causing a precipitate to form. The precipitate was collected by filtration and dried under vacuum at 45°C to yield the title compound as a dark tan solid (413, mg, 87%). LCMS (Method B): R_T = 2.98 min, $[M+M]^+$ = 312.

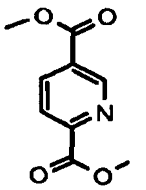
5-(2-Fluoro-4-methylsulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid, Method B

[0229]



Step 1: Pyridine-2,5-dicarboxylic acid dimethyl ester

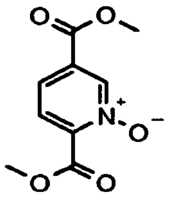
[0230]



[0231] To a suspension of pyridine-2,5-dicarboxylic acid (20 g, 120 mmol) in dichloromethane (396 mL) and DMF (6.6 mL) was added oxalyl chloride (60.96 g, 480 mmol) dropwise over 20 minutes. After 16 hours at ambient temperature, the reaction mixture was *concentrated in vacuo* and the residue azeotroped with toluene. The residue was taken up in cold (0°C) methanol (276 mL) and stirred for 15 minutes. The resultant solution was concentrated *in vacuo* and the residue taken up in ethyl acetate. The mixture was washed with a saturated aqueous solution of sodium bicarbonate, water and brine. A portion of the product was collected as a white precipitate. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a white solid (combined material obtained : 22.93 g, 98%). LCMS (method B): R_T = 2.48 min, $[M+H]^+$ = 196.

Step 2: 1-Oxy-pyridine-2,5-dicarboxylic acid dimethyl ester

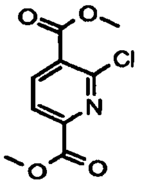
[0232]



[0233] To a cold (0°C) solution of pyridine-2,5-dicarboxylic acid dimethyl ester (22.93 g, 118 mmol) in dichloromethane (472 mL) was added 3-chloroperbenzoic acid (62.5 g, 278 mmol) portionwise. The reaction mixture was allowed to warm to ambient temperature. After stirring for 18 hours, the reaction mixture was concentrated *in vacuo,* and the resultant residue was adsorbed onto HMN and subjected to flash chromatography (Si-PPC, gradient 0% to 100%, ethyl acetate in hexane) to afford the title compound as a pale yellow oil (17.08 g, 69%). LCMS (method B): R_T = 1.64 min, $[M+H]^+$ = 212.

Step 3: 6-Chloro-pyridine-2,5-dicarboxylic acid dimethyl ester

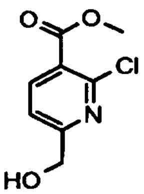
[0234]



[0235] To a solution of 1-oxy-pyridine-2,5-dicarboxylic acid dimethyl ester (17.08 g, 81 mmol) in toluene (450 mL) was added phosphorous oxychloride (8.3 mL, 89 mmol). The reaction mixture was heated to 95°C and stirred for 1.5 hours. The reaction was quenched by the addition of water and the mixture diluted with ethyl acetate. The solution was washed with a saturated aqueous solution of sodium bicarbonate, water and brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a pale yellow solid (11.97 g, 65%) which was used without purification in the next step. LCMS (method B): R_T = 2.77 min, $[M+H]^+$ = 230.

Step 4: 2-Chloro-6-hydroxymethyl-nicotinic acid methyl ester

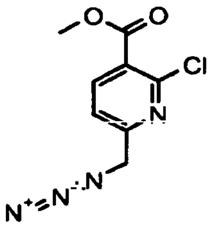
[0236]



[0237] A cold (0°C) suspension of calcium chloride (19.54 g, 176 mmol) and sodium borohydride (4.18 g, 110 mmol) in anhydrous ethanol (176 mL) and anhydrous THF (88 mL) was stirred for 1 hour, after which 6-chloro-pyridine-2,5-dicarboxylic acid dimethyl ester (9.97 g, 44 mmol) was added. After stirring at 0°C for a further 6 hours, the reaction was quenched by the addition of H_2SO_4 (35 mL, 5M). The reaction mixture was diluted with ethyl acetate and filtered through Celite®. The filtrate was washed with 1M NaOH, water and brine, the organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0% to 100%, ethyl acetate in hexane) to afford the title compound as a yellow oil (6.14 g, 69%). LCMS (method B): R_T = 2.34 min, $[M+H]^+$ = 202.

Step 5: 6-Azidomethyl-2-chloro-nicotinic acid methyl ester

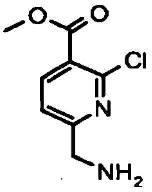
[0238]



[0239] To a cold (0°C) solution of 2-chloro-6-hydroxymethyl-nicotinic acid methyl ester (4.98 g, 24.8 mmol) in dichloromethane (161 mL) was added mesyl chloride (2.5 mL, 29.8 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate, water and brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was taken up in dimethylformamide (62 mL) and sodium azide (4.03 g, 62 mmol) added. After stirring at room temperature for 16 hours, the reaction mixture was cooled to 0°C, quenched with water (ca. 50 mL), and extracted three times with ethyl acetate. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was subjected to flash chromatography (Si-PPC, gradient 0% to 50%, ethyl acetate in hexane) to afford the title compound as a pale yellow oil (4.76 g, 85%). LCMS (method B): R_T = 3.22 min, $[M+H]^+$ = 227.

Step 6: 6-Aminomethyl-2-chloro-nicotinic acid methyl ester

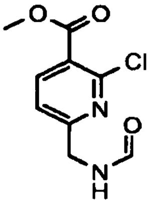
[0240]



[0241] To a solution of 6-azidomethyl-2-chloro-nicotinic acid methyl ester (4.75 g, 21 mmol) in THF (189 mL) and water (3.6 mL) was added triphenylphosphine (11 g, 42 mmol), the reaction mixture was heated at 45°C for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue azeotroped with methanol. The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0% to 10%, methanol in dichloromethane) to afford the title compound as a yellow solid. LCMS (method B): R_T = 2.65 min, $[M+H]^+$ = 201.

Step 7: 2-Chloro-6-formylaminomethyl-nicotinic acid methyl ester

[0242]

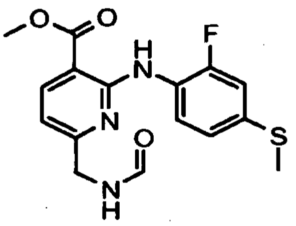


[0243] To a solution of 6-aminomethyl-2-chloro-nicotinic acid methyl ester (740 mg, 3.7 mmol) in formic acid (18.5 mL) was added acetic anhydride (3.7 mL). The reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated *in vacuo* and azeotroped three times with toluene to afford the title compound as a yellow oil (757 mg, 90%) which was used without purification in the next step. LCMS (method B): R_T = 2.20 min, $[M+H]^+$

= 229.

Step 8: 2-(2-Fluoro-4-methylsulfanyl-phenylamino)-6-formylaminomethyl-nicotinic acid methyl ester

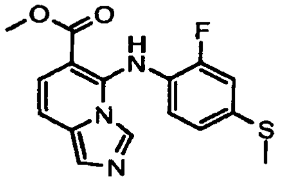
[0244]



[0245] To a solution of 2-chloro-6-formylaminomethyl-nicotinic acid methyl ester (123 mg, 0.54 mmol) in toluene (1.6 mL) was added potassium phosphate (119 mg, 0.76 mmol), 2-fluoro-4-methylsulfanyl-phenylamine (102 mg, 0.65 mmol), tris(dibenzylideneacetone)dipalladium (12.8 mg, 0.014 mmol) and dicyclohexyl-(2',6'-diisopropoxy-biphenyl-2-yl)-phosphane (25 mg, 0.054 mmol). The reaction mixture was degassed with argon then heated at 100°C. After 25 hours, the reaction mixture was cooled, diluted with ethyl acetate and washed with a saturated aqueous solution of ammonium chloride, water then brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was triturated with ethyl acetate to afford the title compound as a bright yellow solid (43 mg, 23%). LCMS (method B): R_T = 3.53 min, $[M+H]^+$ = 350.

Step 9: 5-(2-Fluoro-4-methylsulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester

[0246]



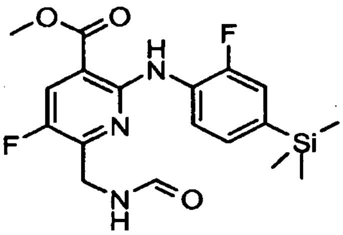
[0247] To a suspension of 2-(2-fluoro-4-methylsulfanyl-phenylamino)-6-formylaminomethyl-nicotinic acid methyl ester (309 mg, 0.89 mmol) in toluene (15.6 mL) was added phosphorous oxychloride (91 µl, 0.98 mmol) and the reaction mixture heated to 95°C and stirred for 1 hour. The cooled reaction mixture was quenched by the addition of water (ca. 2 mL) then concentrated *in vacuo.* The resultant residue was taken up in ethyl acetate and washed with water followed by a saturated aqueous solution of sodium bicarbonate and brine. The organic phase was isolated, dried (Na_2SO_4), filtered, concentrated *in vacuo,* and the residue subjected to flash chromatography (Si-PPC, gradient 0% to 40%, ethyl acetate in hexane) to afford the title compound as a yellow solid (150 mg, 51%). LCMS (method B): R_T = 3.44 min, $[M+H]^+$ = 332.

Step 10: 5-(2-Fluoro-4-methylsulfanyl-phenylaminol-imidazo[1,5-a]pyridine-6-carboxylic acid

[0248] To a solution of 5-(2-fluoro-4-methylsulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (150 mg, 0.45 mmol) in IMS (10 mL) was added sodium hydroxide (0.5 mL, 1M aqueous solution, 0.5 mmol), the reaction mixture heated at 65°C for 1.5 hours. The reaction mixture was concentrated *in vacuo* then taken up in water (ca. 15 mL), the aqueous solution was washed with diethyl ether before the pH was adjusted to pH 3 using 1M HCl, resulting in precipitation of a brown solid. The precipitate was extracted using ethyl acetate, the organic phase was isolated and washed with water followed by brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the title compound as a brown solid (109 mg, 76%). ^1H NMR (CD_3OD): 7.67 (1 H, s), 7.44 (1 H, d, J = 9.53 Hz), 7.39 (1 H, d, J = 0.83 Hz), 7.24 (1 H, dd, J = 9.57, 0.80 Hz), 7.15 (1 H, dd, J = 11.47, 2.12 Hz), 7.02-7.01 (1 H, m), 6.76 (1 H, t, J = 8.49 Hz), 2.49 (3 H, s).

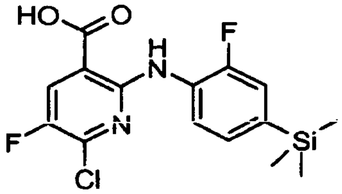
5-Fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-6-formylaminomethyl-nicotinic acid methyl ester

[0249]



Step 1: 6-Chloro-5-fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid

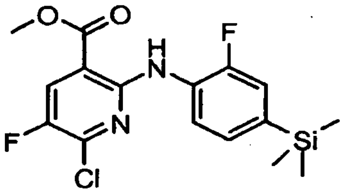
[0250]



[0251] To a cold (-78°C) solution of 2-fluoro-4-trimethylsilanyl-phenylamine (19.2 g, 105 mmol) in anhydrous THF (50 mL) was added a solution of LHMDS (160 mL, 1 M in hexanes, 160 mmol) dropwise over 45 minutes under a nitrogen atmosphere. After 2 hours at -78°C, a solution of 2,6-dichloro-5-fluoro-nicotinic acid (10.5 g, 50 mmol) in anhydrous THF (30 mL) was added. The mixture was stirred at -78°C for 1 hour then allowed to warm to ambient temperature. After 18 hours stirring at ambient temperature the reaction was quenched with water and adjusted to pH 2 by the addition of concentrated HCl. The solution was extracted with ethyl acetate and the organic layer was isolated, washed with water followed by brine, dried (Na_2SO_4), filtered and evaporated *in vacuo.* The resultant residue was triturated with methanol and filtered to afford the title compound as a yellow solid (8.7 g, 49%). LCMS (method B): R_T = 4.92 min, $[M+H]^+$ = 357.

Step 2: 6-Chloro-5-fluoro-2-(2-fluoro-4-trimethylsyilanyl-phenylamino)-nicotinic acid methyl ester

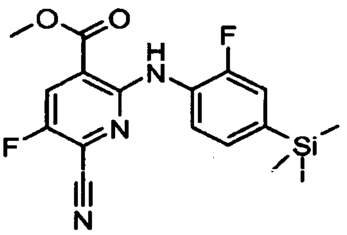
[0252]



[0253] To a suspension of 6-chloro-5-fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid (7.6 g, 21.3 mmol) in dichloromethane (100 mL) and DMF (1 mL) was added oxalyl chloride (9.1 mL, 106.4 mmol) dropwise over 20 minutes. The reaction mixture was stirred at reflux for 18 hours and then concentrated *in vacuo* and the residue azeotroped with toluene. The resultant residue was taken up in cold (0°C) methanol (100 mL). The resultant solution was heated at reflux for 1 hour, then cooled to room temperature and filtered. The precipitate was washed with cold methanol and dried under vacuum at 45°C to give the title compound as a yellow solid (7.3 g, 92%). LCMS (method B): R_T = 5.38 min, $[M+H]^+$ = 371.

Step 3: 6-Cyano-5-fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid methyl ester

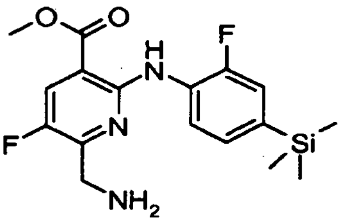
[0254]



[0255] A degassed suspension of 6-chloro-5-fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid methyl ester (7.8 g, 21.2 mmol), zinc (II) cyanide (1.84 g, 15.6 mmol), and Pd(PPh$_3$)$_4$ (2.43 g, 2.12 mmol) in DMF (40 mL) was subjected to microwave irradiation at 150°C for 15 minutes. The reaction mixture was filtered through Celite® and the filtrate diluted with ethyl acetate. The organic phase was washed twice with water and once with brine, dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo.* The resultant residue was triturated with diethyl ether and pentane, and then dried under vacuum to afford the title compound as a yellow solid (6.9 g, 91%). LCMS (method B): R$_T$ = 4.99 min, [M+H]$^+$ = 362.

Step 4: 6-Aminomethyl-5-fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid methyl ester

[0256]



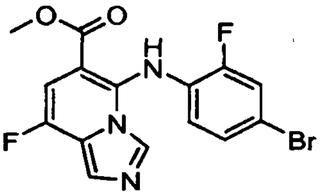
[0257] To a suspension of 6-cyano-5-fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid methyl ester (5.7 g, 15.8 mmol) in methanol (130 mL) was added cobalt (II) chloride (7.5 g, 31.6 mmol). The reaction mixture was stirred for 10 minutes, then cooled to 0°C and sodium borohydride (6.0 g, 158 mmol) was added in small portions over 30 minutes. The reaction mixture was stirred at 0°C for 15 minutes and then at room temperature for 1 hour. The reaction was quenched by addition of concentrated hydrochloric acid (20 mL) and the mixture stirred for 15 minutes. The reaction mixture was filtered to remove a white solid, which was washed with dichloromethane, and the filtrate was concentrated under reduced pressure. The resultant residue was dissolved in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water then brine. The organic phase was isolated, dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo* to afford the title compound as a brown solid (2.0 g, 34%). LCMS (method B): R$_T$ = 2.77 min, [M+H]$^+$ = 366.

Step 5: 5-Fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-6-formylaminomethyl-nicotinic acid methyl ester

[0258] To a solution of 6-aminomethyl-5-fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-nicotinic acid methyl ester (2.0 g, 5.5 mmol) in formic acid (30 mL) at 0°C was added acetic anhydride (6 mL). The reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and the resultant residue azeotroped with toluene, then dissolved in dichloromethane. This organic layer was washed with a saturated aqueous solution of sodium bicarbonate, followed by brine, dried (Na$_2$SO$_4$), filtered and *concentrated in vacuo* to afford the title compound as a dark brown solid (2.1 g, 100%). LCMS (method B): R$_T$ = 4.36 min, [M+H]$^+$ = 394.

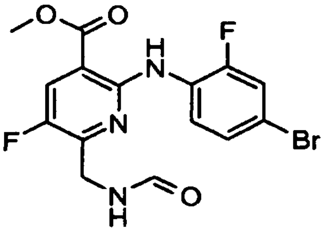
5-(4-Bromo-2-fluoro-phenylamino)-8-fluoro-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester

[0259]



Step 1: 2-(4-Bromo-2-fluoro-phenylamino)-5-fluoro-6-formylaminomethyl-nicotinic acid methyl ester

[0260]



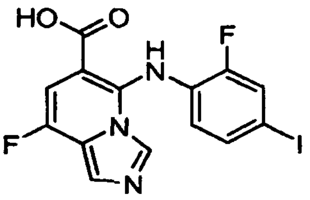
[0261] To a solution of 5-fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-6-formylaminomethyl-nicotinic acid methyl ester (2.6 g, 6.6 mmol) in dichloromethane (65 mL) at -30°C was added NBS (1.2 g, 6.6 mmol). The reaction mixture was stirred at -30°C for 1.5 hours, and then concentrated under reduced pressure The resultant residue was taken up in ethyl acetate and this organic solution was washed with a saturated aqueous solution of sodium bicarbonate, followed by brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to afford the title compound as a brown solid (2.49 g, 95%). LCMS (method B): R_T = 3.79 min, $[M+H]^+$ = 400/402.

Step 2: 5-(4-Bromo-2-fluoro-phenylamino)-8-fluoro-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester

[0262] To a suspension of 2-(4-bromo-2-fluoro-phenylamino)-5-fluoro-6-formylaminomethyl-nicotinic acid methyl ester (2.49 g, 6.2 mmol) in toluene (60 mL) was added phosphorous oxychloride (0.65 mL, 7.0 mmol). The reaction mixture was heated to 90°C and stirred for 1.5 hour before cooling to room temperature and concentrating *in vacuo.* The resultant residue was dissolved in ethyl acetate and washed with water followed by a saturated aqueous solution of sodium bicarbonate and then brine. The organic phase was isolated, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0% to 100%, ether in hexane) to afford the title compound as a yellow solid (692 mg, 29%). LCMS (method B): R_T = 3.97 min, $[M+H]^+$ = 382/384.

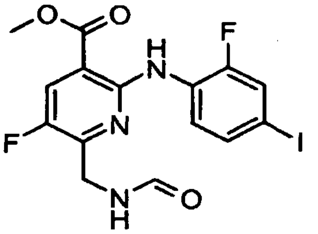
8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid

[0263]



Step 1: 5-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-6-formylaminomethyl-nicotinic acid methyl ester

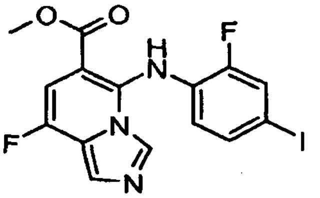
[0264]



[0265] To a solution of 5-fluoro-2-(2-fluoro-4-trimethylsilanyl-phenylamino)-6-formylaminomethyl-nicotinic acid methyl ester (2.4 g, 6.1 mmol) in dichloromethane (15 mL) at 0°C was added IC1 (2.0 g, 12.2 mmol). The mixture was stirred at 0°C for 0.5 hour, then quenched with water, washed with a saturated solution of sodium sulphite followed by brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to afford the title compound as a brown solid (2.7 g, 98%). LCMS (method B): R_T = 3.81 min, $[M+H]^+$ = 448.

Step 2: 8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester

[0266]



[0267] To a suspension of 5-fluoro-2-(2-fluoro-4-iodo-phenylamino)-6-formylaminomethyl-nicotinic acid methyl ester (2.7 g, 6.2 mmol) in toluene (20 mL) was added phosphorous oxychloride (1.1 mL, 12.2 mmol). The reaction mixture was heated at 95°C for 30 minutes. The reaction mixture was cooled to room temperature and then concentrated *in vacuo.* The resultant residue was dissolved in ethyl acetate and washed with water followed by a saturated aqueous solution of sodium bicarbonate, then brine. The organic phase was isolated, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0% to 50%, ethyl acetate in hexane) to afford the title compound as a yellow solid (1.0 g, 39%). LCMS (method B): R_T = 3.97 min, $[M+H]^+$ = 430.

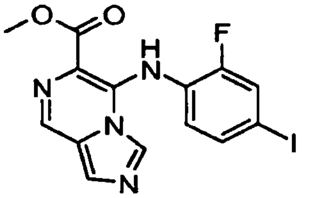
Step 3: 8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid

[0268] To a solution of 8-fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (500 mg, 1.17 mmol) in IMS (10 mL) was added sodium hydroxide (1.75 mL, 1M aqueous solution, 1.75 mmol), the reaction mixture heated at 65°C for 45 min. The reaction mixture was concentrated *in vacuo* and the residue taken up in water. 1N HCl was added to adjust to pH 1. The precipitate formed was filtered off and dried *in* vacuo to give the title compound (435 mg, 90%). LCMS (method B): R_T = 3.47 min, $[M+H]^+$ = 416.

SYNTHESIS OF AZAIMIDAZO[1,5-a]PYRIDINES

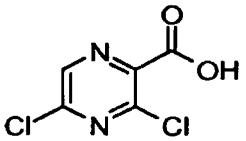
5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid methyl ester

[0269]



Step 1: 3,5-Dichloro-pyrazine-2-carboxylic acid

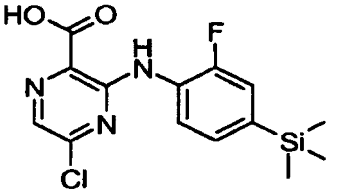
[0270]



[0271] To a solution of diisopropylamine (13.0 mL, 92.6 mmol, 2.3 eq.) in anhydrous THF (300 mL) at -78°C under N_2 was added dropwise a solution of 1.6 M nBuLi in hexanes (57.9 mL, 92.6 mmol, 2.3 eq.). After 1 hour a solution of 2,6-dichloropyrazine in anhydrous THF (6.0 g, 40.3 mmol) was added dropwise over 30 minutes. After stirring at -78°C for 1 hour, the reaction mixture was poured onto crushed dry ice (solid carbon dioxide), and the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was then diluted with water (100 mL) and washed with ethyl acetate (3 x 100 mL). The aqueous layer was cooled to 0°C, acidified with 2N HCl until pH ~ 2, and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo.* The resultant crude was purified by column chromatography (Si-PPC, gradient 0% to 50%, methanol in dichloromethane) to give the desired product as a beige solid (3.16 g, 40.6 %). ^{1}H NMR ($CDCl_3$, 400MHz) δ ppm 8.60 (s, 1H).

Step 2: 5-Chloro-3-(2-fluoro-4-trimethylsilanyl-phenylamino)-pyrazine-2-carboxylic acid

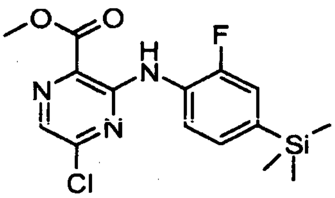
[0272]



[0273] To a solution of 2-fluoro-4-trimethylsilanyl-phenylamine (3.8 g, 20.7 mmol, 2.0 eq) in anhydrous THF (150 mL) at -78°C under N_2 was added dropwise a solution of 1.0 M LHMDS in THF (33.2 mL, 30 mmol, 3.2 eq) over 20 minutes. After 1 hour at -78°C, a solution of 3,5-dichloro-pyrazine-2-carboxylic acid (2.0 g, 10.3 mmol) in anhydrous THF (30 mL) was added. The mixture was stirred at -78°C for 30 minutes, and then stirred at ambient temperature for 18 hours. The mixture was quenched with water and the pH adjusted to pH 2 by the addition of 2 N HCl. The reaction mixture was extracted with ethyl acetate, and the organic layer washed with water and brine, then dried (Na_2SO_4), filtered and evaporated *in vacuo.* The resultant residue was purified by column chromotagraphy (Si-PPC, gradient 20 to 50% ethyl acetate in hexane, followed by 0% to 30%, methanol in dichloromethane) to give the desired compound as a yellow solid (2.95 g, 83.8%). ^{1}H NMR ($CDCl_3$, 400MHz) δ ppm 10.41 (s, 1H), 8.28 (t, J = 7.79 Hz, 1H), 7.93 (s, 1H), 7.40-7.23 (m, 2H), 0.27 (s, 9H).

Step 3: 5-Chloro-3-(2-fluoro-4-trimethylsilanyl-phenylamino)-pyrazine-2-carboxylic acid methyl ester

[0274]

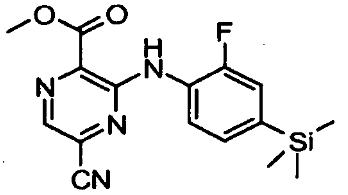


[0275] To a solution of 5-chloro-3-(2-fluoro-4-trimethylsilanyl-phenylamino)-pyrazine-2-carboxylic acid (2.95 g, 8.68 mmol) in methanol (50 mL) and toluene (100 mL) at 0°C under N_2 was added a solution of 2M trimethylsilyldiazomethane in hexanes (9.55 mL, 19.0 mmol, 2.2 eq.), and the reaction mixture was stirred at ambient temperature for 30 minutes.

The reaction mixture was diluted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate, water and brine, then dried (Na_2SO_4), filtered and evaporated *in vacuo.* The resultant residue was purified by column chromotagraphy (Si-PPC, gradient 0 to 50% ethyl acetate in hexane) to give the desired compound as a yellow solid (2.18 g, 71.1%). ^1H NMR ($CDCl_3$, 400MHz) δ ppm 10.54 (s, 1H), 8.36 (t, J = 7.86 Hz, 1H), 8.06 (s, 1H), 7.34-7.26 (m, 2H), 4.05 (s, 3H), 0.28 (s, 9H); LCMS (method D1) R_T = 1.38 min, $[M+H]^+$ = 354.

Step 4: 5-Cyano-3-(2-fluoro-4-trimethylsilanyl-phenylamino)pyrazine-2-carboxylic acid methyl ester

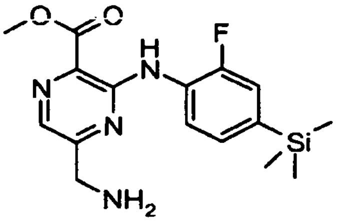
[0276]



[0277] A degassed suspension of 5-chloro-3-(2-fluoro-4-trimethylsilanyl-phenylamino)-pyrazine-2-carboxylic acid methyl ester (1.35 g, 3.82 mmol), zinc (II) cyanide (492.8 mg, 4.2 mmol, 1.1 eq.), and $Pd(PPh_3)_4$ (551.0 mg, 0.48 mmol, 0.12 eq.) in anhydrous dimethylformamide (30 mL) was subjected to microwave irradiation at 150°C for 18 minutes. The reaction mixture was poured into ethyl acetate and then filtered through a pad of Celite®. The pad was rinsed well with ethyl acetate (2x). The combined filtrates were washed with 50% brine (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated *in vacuo.* The crude residue was purified by column chromotagraphy (Si-PPC, gradient 0 to 30% ethyl acetate in hexane) to give a brown oil. Trituration with MeOH afforded the desired compound as an orange solid (1.31 g, 99.8%). ^1H NMR ($CDCl_3$, 400MHz) δ ppm 10.56 (s, 1H), 8.36 (s, 1H), 8.29 (t, J = 7.82 Hz, 1H), 7.37-7.27 (m, 2H), 4.10 (s, 3H), 0.29 (s, 9H); LCMS (method D1): R_T = 1.28 min, $[M+H]^+$ = 345.

Step 5: 5-Aminomethyl-3-(2-fluoro-4-trimethylsilanyl-phenylamino)-pyrazine-2-carboxylic acid methyl ester

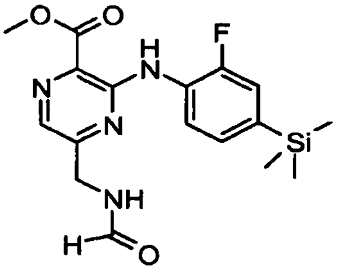
[0278]



[0279] To a solution of 5-cyano-3-(2-fluoro-4-trimethylsilanyl-phenylamino)-pyrazine-2-carboxylic acid methyl ester (600 mg, 1.74 mmol) in concentrated glacial acetic acid (12 mL) was added 10% Pd on carbon (120 mg). The reaction mixture was evacuated with vacuum and purged with H_2 (3x), then stirred under an atmosphere of H_2 for 3.5 hours. The reaction mixture was then filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* to give the desired product as the HOAc salt. LCMS (method C): R_T = 2.51 min, $[M+H]^+$ = 349.

Step 6: 3-(2-Fluoro-4-trimethylsilanyl-phenylamino)-5-formylaminomethyl-pyrazine-2-carboxylic acid methyl ester

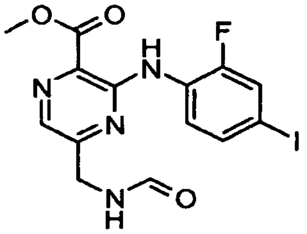
[0280]



[0281] A solution of 5-aminomethyl-3-(2-fluoro-4-trimethylsilanyl-phenylamino)-pyrazine-2-carboxylic acid methyl ester (800 mg, 2.30 mmol) from above in formic acid (12 mL) and acetic anhydride (4 mL) was stirred at ambient temperature under N_2 for 1.5 hour. The reaction mixture was concentrated *in vacuo,* and the residue was azeotroped with toluene. The resultant residue was diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium bicarbonate, water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a yellow foam (850 mg, 98.3%). LCMS (method D1): R_T = 1.09 min, $[M+H]^+$ = 377.

Step 7: 3-(2-Fluoro-4-iodo-phenylamino)-5-formylaminomethyl-pyrazine-2-carboxylic acid methyl ester

[0282]



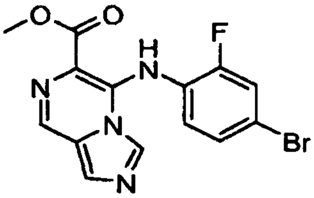
[0283] To a cold (0°C) solution of 3-(2-fluoro-4-trimethylsilanyl-phenylamino)-5-formylaminomethyl-pyrazine-2-carboxylic acid methyl ester (480 mg, 1.28 mmol) in dichloromethane (13 mL) under N_2 was added dropwise a solution of 1M iodine monochloride in dichloromethane (3.0 mL, 3.0 mmol, 2.4 eq), and the mixture was stirred at 0°C for 1.5 hour. The reaction was quenched by addition of a saturated aqueous solution of sodium thiosulfate (~3 mL). After stirring for 10 minutes the reaction mixture was poured into ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate, water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to afford the desired product as a yellow solid (548 mg, 99%). LCMS (method C): R_T = 2.65 min, $[M+H]^+$ = 431.

Step 8: 5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid methyl ester

[0284] To a suspension of 3-(2-fluoro-4-iodo-phenylamino)-5-formylaminomethyl-pyrazine-2-carboxylic acid methyl ester (480 mg, 1.12 mmol) in toluene (18 mL) was added phosphorous oxychloride (0.42 mL, 4.4 mmol, 4.0 eq.), and the reaction mixture was heated at 95°C for 1 hour. The reaction mixture was cooled to RT and then quenched with a saturated aqueous solution of sodium bicarbonate (2 mL). The resultant residue was dissolved in ethyl acetate and washed with water and brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0% to 20%, methanol in ethyl acetate) to give a yellow oil. Crystallization from dichloromethane - ether - hexane afforded the desired product as a yellow solid (190 mg, 41.3%). LCMS (method C): R_T = 2.45 min, $[M+H]^+$ = 413.

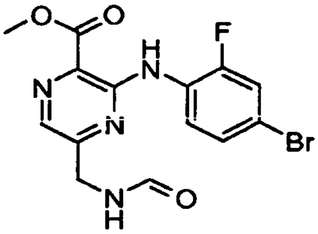
5-(4-Bromo-2-fluoro-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid methyl ester

[0285]



Stop 1: 3-(4-Bromo-2-fluoro-phenylamino)-5-formylaminomethyl-pyrazine-2-carboxylic acid methyl ester

[0286]



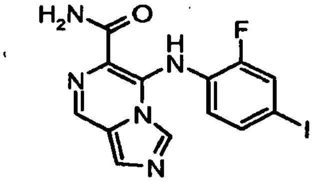
[0287] To a -30 °C solution of 3-(2-fluoro-4-trimethylsilanyl-phenylamino)-5-formylaminomethyl-pyrazine-2-carboxylic acid methyl ester (1.84 g, 4.89 mmol) in dichloromethane (50 mL) under N_2 was added NBS (0.96 g, 5.38 mmol, 1.1 eq.), and the reaction mixture was stirred at -30 °C for 3h. More NBS (0.96g, 5.38 mmol, 1.1 eq.) was added, and the reaction mixture was allowed to stand at 0 °C for 18h. The reaction mixture was diluted with ethyl acetate (250 mL). The organic layer was washed with saturated aqueous solution of sodium bicarbonate, water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The crude material was triturated with methanol to afford the desired product as a yellow solid (1.50 g, 80.1%). LCMS (method C): R_T = 2.51 min, $[M+H]^+$ = 383 / 384.

Step 2: 5-(4-Bromo-2-fluoro-phenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid methyl ester

[0288] To a suspension of 3-(4-bromo-2-fluoro-phenylamino)-5-formylamino-methyl-pyrazine-2-carboxylic acid methyl ester (1.40 g, 3.65 mmol) in toluene (100 mL) was added phosphorous oxychloride (1.50 mL, 16.1 mmol, 4.4 eq.), and the reaction mixture was heated at 95 °C under N_2 for 1 hour. The reaction mixture was cooled to RT and then quenched with saturated aqueous solution of sodium bicarbonate (20 mL). The resultant residue was dissolved in ethyl acetate and washed with water and brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 70 to 100% ethyl acetate in hexane, followed by 0% to 2% methanol in ethyl acetate) to give an orange oil. Crystallization from ethyl acetate - hexane afforded the desired product as an orange solid (1.26 g, 94.3%). LCMS (method D1): R_T = 0.86 min, $[M+H]^+$ = 366 / 367.

5-(2-Fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide

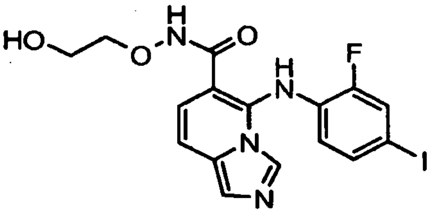
[0289]



[0290] To a solution of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid (64.0 mg, 0.16 mmol) in anhydrous THF (3.6 mL) was added HOBt (56.5 mg, 0.42 mmol, 2.6 eq), DIPEA (0.073 mL, 0.42 mmol, 2.6 mmol), and EDCI (67.8 mg, 0.35 mmol, 2.2 eq), and the reaction mixture was stirred at room temperature under N_2 for 2h. Concentrated aqueous ammonium hydroxide solution (0.50 mL) was added and the reaction mixture was stirred at room temperature for 20h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with a saturated aqueous solution of ammonium chloride, water and brine. The organic layer was isolated and dried (Na_2SO_4), filtered, and concentrated in *vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0 to 20% methanol in dichloromethane) to give an oil. Crystallization from DCM - ether - hexane afforded the title compound as a beige solid (9.9 mg, 16.0 %). ^{1}H NMR (MeOD, 400MHz) δ ppm 8.74 (s, 1H), 7.86(s, 1H), 7.79 (s, 1H), 7.62 (dd, J = 10.4 Hz, 2.0 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 6.59 (t, J = 8.4 Hz, 1H); LCMS (method D1): R_T = 0.84 min, $[M+H]^+$ = 398.

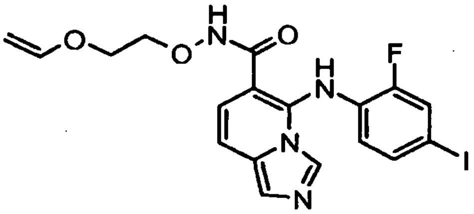
EXAMPLE 5: 5-(2-Fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxyethoxy)-amide

[0291]



Step 1, Method A: 5-(2-Fluoro-4-iodophenylamino)-imidazo[1.5-a]pyridine-6-carboxylic acid (2-vinyloxyethoxy)-amide

[0292]



[0293] To a solution of 5-(2-fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2.10 g, 5.29 mmol) and O-(2-vinyloxyethyl)-hydroxylamine (0.87 g, 8.46 mmol) in DMF (30 mL) was added EDCI hydrochloride (1.31 g, 6.90 mmol), HOBt (0.93 g, 6.90 mmol) and DIPEA (1.17 mL, 6.90 mmol). The reaction mixture was stirred at room temperature for 5 hours before being concentrated *in vacuo.* The resultant residue was dissolved in 1:1 tert-butylmethylether : ethyl acetate (20 mL) and aqueous saturated sodium hydrogen carbonate solution (20 mL) was added. The resultant mixture was sonicated until a precipitate formed, the precipitate was collected by filtration and dried *in vacuo* at 45°C to yield the title compound as a tan solid (1.55 g, 60%). LCMS (Method B): R_T = 2.80 min, $M+H^+$ = 483.

Step 1, Method B: 5-(2-Fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxyethoxy)-amide

[0294] To a solution of 5-(2-fluoro-4-iodophenylamino)imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (1.5 g, 3.64 mmol) and O-(2-vinyloxyethyl)hydroxylamine (749 mg, 7.28 mmol) in THF (30 mL) at 0°C was added lithium bis(trimethylsilyl)amide as a solution in THF (18 mL, 1 M, 18 mmol) over 5 minutes. The reaction mixture was stirred at ~0°C for 1 hour before being quenched with saturated aqueous ammonium chloride. Volatile solvents were removed *in vacuo* and then diethyl ether (10 mL) and ethyl acetate (20 mL) added. The resultant mixture was sonicated causing a precipitate to form which was filtered off to give the title compound as a yellow solid (1.07 g, 61%). LCMS (Method B): R_T = 2.79 min, $M+H^+$ = 483.

Step 1, Method C: 5-(2-Fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxyethoxy)-amide

[0295] To a mechanically stirred solution of 5-(2-fluoro-4-iodophenylamino)imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (82.17 g, 0.2 mol) and O-(2-vinyloxyethyl) hydroxylamine (40.73 g, 0.382 mol) in dry THF (1.27 L) at 5°C under N_2 atmosphere, was added lithium bis(trimethylsilyl)amide as a solution in THF (1 L, 1 M, 1 mol) over 1 hr, maintaining the temperature below 10°C. The reaction mixture was stirred at 0-5 °C for 20 minutes before being quenched with addition water (200 ml) and saturated saline (350 mL). Volatile solvents were removed *in vacuo* and the residue diluted with water (1.5 L) and extracted 2-methyl tetrahydrofuran (3 x1 L). The organic layers were washed water (500mL), saturated saline (500 mL), dried (Na_2CO_3) and absorbed onto silica gel (200g) and purified on silica gel (400g) using ethyl acetate as eluent. The resultant crude product was triturated with tert-butyl methyl ether (400 mL) to yield the title compound as a brown solid (58.36 g, 60%). LCMS (Method B): R_T = 2.79 min, $[M+H]^+$ = 483.

Step 2, Method A: 5-(2-Fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxyethoxy)-amide

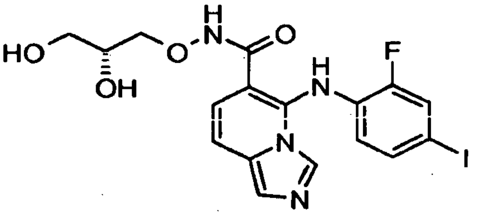
[0296] To a suspension of 5-(2-fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxyethoxy)-amide (2.87 g, 5.95 mmol) in methanol (45 mL) was added aqueous hydrochloric acid (11.9 mL, 1M, 11.9 mmol). The reaction mixture was stirred at room temperature for 45 minutes during which time the solids dissolved. The reaction mixture was concentrated *in vacuo* to remove the methanol. The resultant solution was diluted with 1:1 tert-butylmethylether : ethyl acetate (20 mL) and aqueous saturated sodium hydrogen carbonate solution (20 mL) added. The resultant mixture was sonicated until a precipitate formed and the precipitate was collected by filtration and dried *in vacuo* at 45°C to yield the title compound as a yellow solid (2.5 g, 92%). LCMS (Method A): R_T = 5.58 min, $M+H^+$ = 457. ^{1}H NMR (DMSO-d_6, 400MHz) 8.05 (1 H, s), 7.58 (1 H, dd, J = 10.69, 1.92 Hz), 7.43 (1 H, s), 7.39 (1 H, d, J = 9.33 Hz), 7.31-7.28 (1 H, m), 6.89 (1 H, d, J = 9.31 Hz), 6.34 (1 H, t, J = 8.68 Hz), 4.64 (1 H, s), 3.64 (2 H, t, J = 4.78 Hz), 3.46 (2 H, m).

Step 2, Method B: 5-(2-Fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxyethoxy)-amide

[0297] To a suspension of 5-(2-fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxyethoxy)-amide (58.36 g, 0.12 mol) in methanol (600 mL) was added aqueous hydrochloric acid (242 mL, 1M, 0.242 mol). The reaction mixture was stirred and warmed to 45°C for 1hr during which time the solids dissolved. The reaction mixture was then cooled to room temperature, and concentrated *in vacuo* to remove the methanol. The resultant residue was treated with aqueous saturated sodium hydrogen carbonate and stirred at room temperature for 1 hr before collecting crude product by filtration, and drying at 55°C over phosphorus (V) oxide under vacuum for 24 hr. The crude product was crystallized from IPA:H_2O (1:1, v/v) (800mL) with slow cooling and mechanical stirring. The product was collected by filtration and washed cold IPA:H_2O (1:1, v/v) (100 mL) before being dried *in vacuo* at 55°C to yield the title compound as a light brown solid (50.2 g, 90%). LCMS (Method A): R_T = 5.58 min, $[M+H]^+$ = 457. ^{1}H NMR (DMSO-d_6, 400MHz) 8.05 (1 H, s), 7.58 (1 H, dd, J = 10.69, 1.92 Hz), 7.43 (1 H, s), 7.39 (1 H, d, J = 9.33 Hz), 7.31-7.28 (1 H, m), 6.89 (1 H, d, J = 9.31 Hz), 6.34 (1 H, t, J = 8.68 Hz), 4.64 (1 H, s), 3.64 (2 H, t, J = 4.78 Hz), 3.46 (2 H, m).

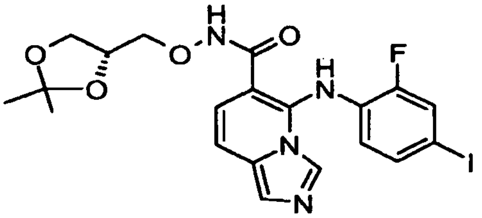
EXAMPLE 6: 5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((R)-2,3-dihydroxy-propoxy)-amide

[0298]



Step 1: 5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2,2-dimethyl-[1,3]dioxolan-4-yl-methoxy)-amide

[0299]



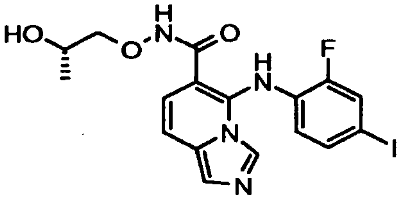
[0300] To a solution of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (326 mg, 0.82 mmol) in THF (4.1 ml) was added O-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine (362 mg, 2.46 mmol), DIPEA (1.26 ml, 7.4 mmol), HOBt (327 mg, 2.46 mmol) and EDCI (471 mg, 2.46 mmol), the mixture stirred for 18 hours at ambient temperature. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate followed by water and then brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* Purification of the resultant residue by flash chromatography (Si-PPC, gradient 0% to 10%, methanol in dichloromethane) afforded the title compound as a pale yellow solid (364 mg, 84%). LCMS (method B): R_T = 2.58 min, $[M+H]^*$ = 527.

Step 2: 5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((R)-2,3-dihydroxy-propoxy)-amide

[0301] A solution of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-amide (364 mg, 0.7 mmol) in methanol (0.5 ml) and dichloromethane (0.5ml) was loaded onto an SCX-2 cartridge. The cartridge was flushed with methanol and the desired product was eluted using a 2M solution of ammonia in methanol. The appropriate fractions were combined and concentrated under reduced pressure and the residue was azeotroped with dichloromethane. Purification of the resultant residue by flash chromatography (Si-PPC, gradient 0% to 10%, methanol in dichloromethane) followed by preparative HPLC (Gemini 5 micron C_6-Phenyl 250x21.20mm column, 20 mmol Et_3N per litre solvent, gradient acetonitrile/ water, 5 to 98%, ramp time 25 minutes) afforded the title compound as a yellow solid (77.6 mg, 23%). LCMS (method A): R_T = 5.13 min, $[M+H]^+$ = 487. ^1H NMR (DMSO-d_6): 8.01 (1 H, s), 7.58 (1 H, dd, J = 10.68, 1.92 Hz), 7.42 (1 H, s), 7.38 (1 H, d, J = 9.34 Hz), 7.30 (1 H, dd, J = 8.43, 1.82 Hz), 6.91 (1 H, d, J = 9.32 Hz), 6.32 (1 H, t, J = 8.68 Hz), 3.72-3.67 (1H, m), 3.60-3.51 (2 H, m), 3.30 (2 H, d, J = 4.94 Hz).

EXAMPLE 7: 5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-*a*]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide

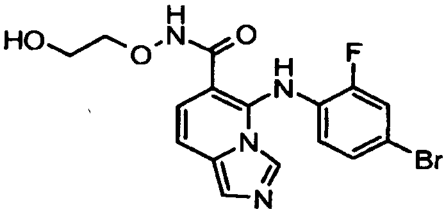
[0302]



[0303] To a solution of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (130 mg, 0.33 mmol) in THF (1.7 mL) was added (S)-1-aminooxy-propan-2-ol hydrochloride (84 mg, 0.66 mmol)), DIPEA (0.23 mL, 1.32 mmol), HOBt (88 mg, 0.66 mmol) and EDCI (126 mg, 0.66 mmol). After 18 hours stirring at ambient temperature, further (S)-1-aminooxy-propan-2-ol hydrochloride (84 mg, 0.66 mmol), DIPEA (0.23 mL, 1.32 mmol), HOBt (88 mg, 0.66 mmol) and EDCI (126 mg, 0.66 mmol) and THF (1.7 mL) were added. The reaction mixture was stirred at ambient temperature for a further 5 hours. The reaction mixture was loaded onto an Isolute ® SCX-2 cartridge. The cartridge was then washed with methanol and the desired compound was eluted using a 2M solution of ammonia in methanol. Appropriate fractions were combined and concentrated under reduced pressure and the residue azeotroped with dichloromethane. The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0 to 10%, methanol in dichloromethane) to afford the title compound as a yellow solid (17 mg, 11%). LCMS (method A): R_T = 6.01 min, $[M+H]^+$ = 471. ^1H NMR (DMSO-d_6): 8.07 (1 H, s), 7.58 (1 H, dd, J = 10.71, 1.92 Hz), 7.43 (1 H, s), 7.38 (1 H, d, J = 9.31 Hz), 7.31-7.28 (1 H, m), 6.89 (1 H, d, J = 9.31 Hz), 6.35 (1 H, t, J = 8.68 Hz), 3.69-3.60 (1 H, m), 3.45-3.38 (2 H, m), 0.96 (3 H, d, J = 6.35 Hz).

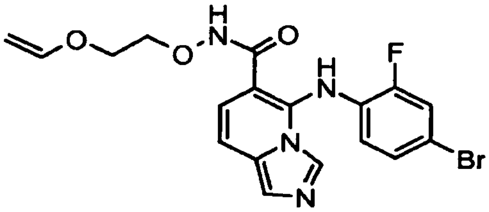
EXAMPLE 8: 5-(4-Bromo-2-fluorophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxyethoxy)-amide

[0304]



Step 1: 5-(4-Bromo-2-fluorophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxyethoxy)-amide

[0305]



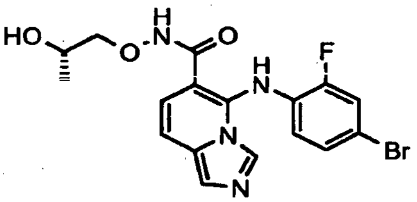
[0306] To a solution of 5-(4-Bromo-2-fluorophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2.0 g, 5.7 mmol) and O-(2-vinyloxyethyl)-hydroxylamine (0.71 g, 6.8 mmol) in DMF (44 mL) was added EDCI hydrochloride (1.42 g, 7.41 mmol), HOBt (1.0 g, 7.41 mmol) and DIPEA (0.97 mL, 5.69 mmol). The reaction mixture was stirred at room temperature for 3 hours before being concentrated *in vacuo.* The resultant residue was dissolved in 1:1 diethylether : ethyl acetate (30 mL) and aqueous saturated sodium hydrogen carbonate solution (30 mL) was added. The resultant mixture was sonicated until a precipitate formed. The precipitate was collected by filtration and washed with 1:1 diethylether : ethyl acetate to yield the title compound as a tan solid (1.33 g, 53%). LCMS (Method B): R_T = 2.78 min, M+H$^+$ = 435/437.

Step 2: 5-(4-Bromo-2-fluorophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxyethoxy)-amide

[0307] To a suspension of 5-(4-Bromo-2-fluorophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxyethoxy)-amide (1.33 g, 3.05 mmol) in methanol (40 mL) was added aqueous hydrochloric acid (6.7 mL, 1M, 6.7 mmol). The reaction mixture was stirred at room temperature for 30 minutes then concentrated *in vacuo* to remove the methanol. The resultant residue was dissolved in 1:1 diethylether : ethyl acetate (30 mL) and aqueous saturated sodium hydrogen carbonate solution (30 mL) added. The resultant mixture was sonicated until a precipitate formed, the precipitate collected by filtration and washed with water then diethyl ether to yield the title compound as a yellow solid (1.12 g, 90%). LCMS (method A): R_T = 5.22 min, [M+H]$^+$= 409/411. ^{1}H NMR (DMSO-d$_6$, 400MHz) 9.20 (1 H, s), 8.07 (1 H, s), 7.51 (1 H, dd, J = 10.86, 2.22 Hz), 7.44 (1 H, s), 7.40 (1 H, d, J = 9.33 Hz), 7.16 (1 H, ddd, J = 8.61, 2.20, 1.07 Hz), 6.89 (1 H, d, J = 9.31 Hz), 6.50 (1 H, t, J = 8.84 Hz), 4.63 (1 H, s), 3.65 (2 H, t, J = 4.79 Hz), 3.46 (3 H, s).

EXAMPLE 9: 5-(4-Bromo-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide

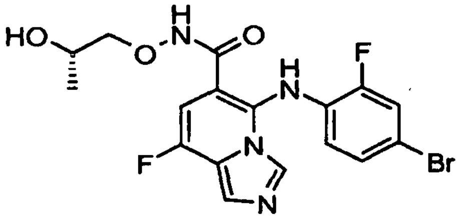
[0308]



[0309] To a solution of 5-(4-bromo-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (271 mg, 0.77 mmol) in dioxane (3.9 mL) was added HOBT (306 mg, 2.3 mmol) and EDCI (442 mg, 2.3 mmol). The reaction mixture was stirred at ambient temperature for 30 minutes then (S)-1-aminooxy-propan-2-ol hydrochloride (294 mg, 2.3 mmol) and DIPEA (1.2 mL, 6.9 mmol) were added, the mixture was then stirred for 60 hours at ambient temperature. The reaction mixture was diluted with ethyl acetate then washed with a saturated aqueous solution of sodium bicarbonate followed by water and brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0 to 100%, ethyl acetate in dichloromethane, then gradient 0 to 10%, methanol in dichloromethane) to afford the title compound as a green/yellow solid (80 mg, 25%). LCMS (method A): R_T = 5.71 min, [M+H]$^+$= 423/425. ^{1}H NMR (DMSO-d$_6$): 8.10 (1 H, s), 7.51 (1 H, dd, J = 10.87, 2.22 Hz), 7.43 (1 H, s), 7.39 (1 H, d, J = 9.31 Hz), 7.18-7.14 (1 H, m), 6.88 (1 H, d, J = 9.31 Hz), 6.51 (1 H, t, J = 8.85 Hz), 4.69 (1 H, s), 3.68-3.59 (1 H, m), 3.42 (2 H, d, J = 5.81 Hz), 0.95 (3 H, d, J = 6.35 Hz).

EXAMPLE 10: 5-(4-Bromo-2-fluoro-phenylamino)-8-fluoro-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide

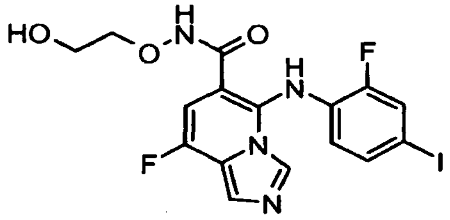
[0310]



[0311] To a solution of 5-(4-bromo-2-fluoro-phenylamino)-8-fluoro-imidazo[1,5-a]pyridine-6-carboxylic acid methyl ester (351 mg, 0.92 mmol) in IMS (10 mL) was added sodium hydroxide (1.0 mL, 1M aqueous solution, 1.0 mmol). The reaction mixture was heated at 65°C for 1 hour, and then concentrated *in vacuo.* The resultant residue was azeotroped with toluene and then suspended in dioxane. EDCI (353 mg, 1.84 mmol) and HOBt (248 mg, 1.84 mmol) were added and the mixture was stirred at room temperature for 20 minutes. (S)-1-Aminooxy-propan-2-ol hydrochloride (235 mg, 1.84 mmol) and DIPEA (0.63 mL, 3.68 mmol) were added and the resultant mixture was stirred for 18 hours, before being concentrated under reduced pressure. The resultant residue was taken up in ethyl acetate then washed with a saturated aqueous solution of sodium bicarbonate followed by water and brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0 to 10%, methanol in dichloromethane) to give a pale yellow solid (124 mg), which was further purified by preparative HPLC (Gemini 5 micron C_{18} 250x21.20mm column, 0.1 % formic acid, gradient acetonitrile/ water, 5 to 85%, ramp time 15 minutes) to afford the title compound as an off-white solid (70 mg, 17%). LCMS (method A): R_T = 7.83 min, $[M+H]^+$= 441/443. ^1H NMR ($CDCl_3$): 9.45 (1 H, s), 8.99 (1 H, s), 7.76 (1 H, d, J = 2.95 Hz), 7.59 (1 H, s), 7.29 (1 H, dd, J = 10.10, 2.16 Hz), 7.12 (1 H, d, J = 8.52 Hz), 6.50 (1 H, d, J = 10.18 Hz), 6.41 (1 H, t, J = 8.54 Hz), 4.03 (1 H, t, J = 7.52 Hz), 3.94 (1 H, d, J = 11.57 Hz), 3.70 (1 H, t, J = 10.24 Hz), 1.14 (3 H, d, J = 6.46 Hz).

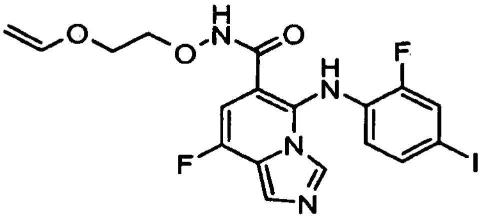
EXAMPLE 11: 8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide

[0312]



Step 1: 8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxy-ethoxy)-amide

[0313]



[0314] 8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (0.20 g, 0.48 mmol), O-(2-

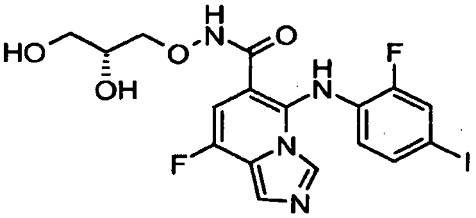
vinyloxyethyl)-hydroxylamine (55 mg, 0.53 mmol), EDCI (102 mg, 0.53 mmol), HOBt (72 mg, 0.53 mmol) and DIPEA (90 μL, 0.53 mmol) were dissolved in DMF (10 mL) and the reaction mixture stirred at room temperature for 16 hours before being concentrated *in vacuo.* The resultant residue was dissolved in ethyl acetate (10 mL), washed with aqueous saturated sodium bicarbonate solution (10 mL) and the aqueous fraction extracted twice with ethyl acetate (2 × 10 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 0-10% methanol in DCM) to yield the title compound as a pale yellow solid (200 mg, 83%). LCMS (Method B): R_T = 3.41 min, $[M+H]^+$ = 501.

Step 2: 8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-alpyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide

[0315] A solution of 8-fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxy-ethoxy)-amide (200 mg, 0.39 mmol) in methanol (1 mL) was loaded onto an SCX-2 column. The column was washed with methanol (10 mL) then the product was then eluted with ammonia in methanol (20 mL, 2M), the appropriate fractions were concentrated *in vacuo.* The resultant residue was subjected to reverse phase preperative HPLC (10-90% acetonitrile/water 0.1% formic acid, Phenominex gemini PhC6, 5 micron, 250 × 20 mm). The resultant product was dissolved in ethyl acetate (5mL) and washed with aqueous saturated sodium bicarbonate solution (10 mL). The aqueous fraction was extracted twice with ethyl acetate (2 × 10 mL) and the combined organics were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a white solid (88 mg, 39%). LCMS (Method A): R_T = 7.71 min, $[M+H]^+$ = 475. ^1H NMR (DMSO-d_6): 8.20 (1 H, s), 7.60 (1 H, s), 7.57 (1 H, dd, J = 10.73, 1.96 Hz), 7.26 (1 H, dd, J = 8.43, 1.82 Hz), 6.82 (1 H, d, J = 11.14 Hz), 6.30 (1 H, t, J = 8.71 Hz), 3.65 (2 H, t, J = 4.77 Hz), 3.45 (2 H, t, J = 4.68 Hz).

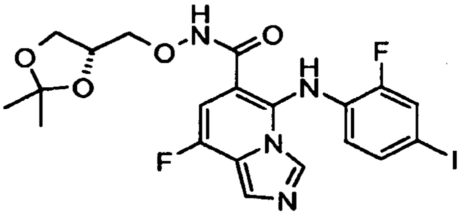
EXAMPLE 12: 8-Fluoro-5-(2-fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((*R*)-2,3-dihydroxy-propoxy)-amide

[0316]



Step 1: 8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-amide

[0317]



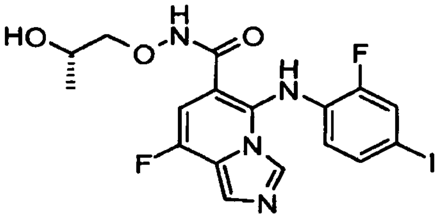
[0318] 8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (235 mg, 0.57 mmol), O-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-hydroxylamine (92 mg, 0.62 mmol), EDCI (120 mg, 0.62 mmol), HOBt (84 mg, 0.62 mmol) and DIPEA (0.1 mL, 0.62 mmol) were dissolved in DMF (10 mL) and the reaction mixture stirred at room temperature for 72 hours before being concentrated *in vacuo.* The resultant residue was dissolved in ethyl acetate (10 mL), washed with aqueous saturated sodium bicarbonate solution (10 mL) and the aqueous fraction extracted twice with ethyl acetate (2 × 10 mL). The combined organic fractions were washed with brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (SiO_2, gradient 0-10% methanol in DCM) to yield the title compound as a pale yellow solid (298 mg, 97%). LCMS (Method B): R_T = 3.34 min, $[M+H]^+$ = 545.

Step 2: 8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((*R*)-2,3-dihydroxy-propoxy)-amide

[0319] To a solution of 8-fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-amide (298 mg, 0.55 mmol) in methanol (5 mL) was added hydrochloric acid in dioxane (2 mL, 4N, 8.0 mmol). The reaction mixture was stirred at room temperature for 1 hour then concentrated *in vacuo.* The resultant residue was dissolved in ethyl acetate (5 mL), washed with aqueous saturated sodium bicarbonate solution (10 mL) and the aqueous fraction extracted twice with ethyl acetate (2 × 5 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The resultant residue was subjected to reverse phase preperative HPLC (10-90% acetonitrile/water 0.1% formic acid, Phenominex gemini PhC6, 5 micron, 250 × 20 mm). The resultant product was dissolved in ethyl acetate (5mL) and washed with aqueous saturated sodium bicarbonate solution (10 mL). The aqueous fraction was extracted twice with ethyl acetate (2 × 10 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a white solid (83 mg, 30%). LCMS (Method A): R_T = 7.11 min, $[M+H]^+$ = 505. ^1H NMR (DMSO-d_6): 11.63 (1 H, s), 8.97 (1 H, s), 8.22 (1 H, d, J = 3.06 Hz), 7.61 (1 H, s), 7.57 (1 H, dd, J = 10.74, 1.93 Hz), 7.26 (1 H, d, J = 8.50 Hz), 6.82 (1 H, d, J = 11.09 Hz), 6.32 (1 H, t, J = 8.74 Hz), 3.72-3.65 (1 H, m), 3.59-3.50 (2 H, m), 3.29 (2 H, m).

EXAMPLE 13: 8-Fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide

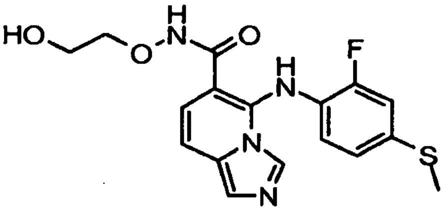
[0320]



[0321] A suspension of 8-fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (100 mg, 0.23 mmol), HATU (130 mg, 0.34 mmol), DIPEA (0.06 mL, 0.34 mmol) and (S)-2-hydroxy-propoxy-amide hydrochloride (44 mg, 0.34 mmol) in THF (1 mL) was stirred at room temperature for 18 hours. The reaction mixture was partitioned between ethyl acetate (5 mL) and 1M HCl, the organic layer was isolated and washed with saturated aqueous $NaHCO_3$ (2 x 5 mL) and brine (2 x 5mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The resultant residue was subjected to reverse-phase preparative HPLC (Gemini 5 micron C_{18} 250x21.20mm column, 0.1% formic acid, gradient acetonitrile/ water, 5 to 98%, ramp time 20 minutes) to afford the title compound as a yellow solid (13 mg, 8%). LCMS (method A): R_T = 8.13 min, $[M+H]^+$ = 489. 1H NMR (DMSO-d_6):11.51 (1 H, broad), 8.95 (1 H, broad), 8.25 (1 H, s), 7.60 (1 H, s), 7.55 (1 H, d, J = 10.7 Hz), 7.27 (1 H, d, J = 8.4 Hz), 6.82 (1 H, d, J = 11.1 Hz), 6.32 (1 H, t, J = 8.8 Hz), 4.66 (1 H, broad), 3.64 (1 H, m), 3.43 (2 H, d, J = 5.8 Hz), 0.94 (3 H, d, J = 6.3 Hz).

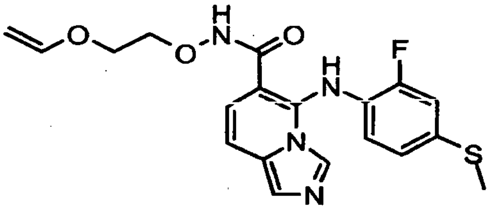
EXAMPLE 14: 5-(2-Fluoro-methanesulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide

[0322]



Step 1: 5-(2-Fluoro-4-methanesulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxy-ethoxy)-amide

[0323]



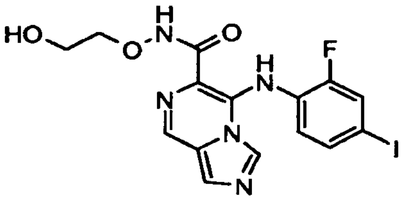
[0324] To a mixture of 5-(2-fluoro-4-methanesulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (400 mg, 1.26 mmol), O-(2-vinyloxyethyl)-hydroxylamine (260 mg, 2.52 mmol) and HOBt (221 mg, 1.64 mmol) in DMF (5 mL) was added EDCI hydrochloride (312 mg, 1.64 mmol), and DIPEA (0.285 mL, 1.64 mmol) and the mixture stirred at room temperature for 20 hours. The products were partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was separated and washed with brine, then dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound (263 mg, 52%). LCMS (Method B): R_T 2.64 $[M+H]^+$ 403.

Step 2: 5-(2-Fluoro-4-methanesulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide

[0325] To a solution 5-(2-fluoro-4-methanesulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxy-ethoxy)-amide (263 mg, 0.65 mmol) in methanol (10 mL) was added 1M hydrochloric acid (1 mL, 1 mmoL) and the mixture stirred at room temperature for 2 hours. The resultant mixture was concentrated *in vacuo* before being partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. The organic layer was separated, washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was triturated with ethyl acetate and the solid collected by filtration was subjected to flash chromatography (Si-PPC, gradient 0 to 10%, methanol in DCM) to afford the title compound as a tan solid (123mg, 50%). LCMS (method A): R_T = 5.15 min, $[M+H]^+$ = 377. ^1H NMR (DMSO-d_6, 400MHz) 11.54 (1H, s), 9.39 (1 H, s), 7.93 (1 H, s), 7.39 (1 H, s), 7.32 (1 H, d, J = 9.36 Hz), 7.16 (1 H, dd, J = 11.86, 2.13 Hz), 6.93-6.88 (2 H, m), 6.57 (1 H, t, J = 8.65 Hz), 4.62 (1 H, s), 3.66 (2 H, t, J = 4.85 Hz), 3.45 (2 H, t, J = 4.77 Hz), 2.40 (3 H, s).

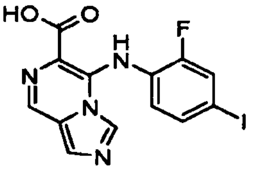
EXAMPLE 15: 5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid (2-hydroxy-ethoxy)-amide

[0326]



Step 1: 5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid

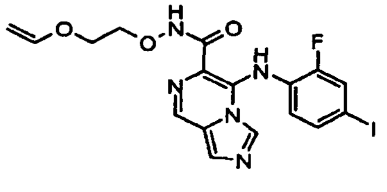
[0327]



[0328] To a solution of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid methyl ester (140 mg, 0.34 mmol) in anhydrous 1,2-dichloroethane (2.5 mL) was added trimethyltin hydroxide (215 mg, 1.19 mmol, 3.5 eq.). The reaction mixture was heated at 85°C for 1 hour and then cooled to RT. The reaction mixture was concentrated in *vacuo,* and the crude residue was diluted with ethyl acetate. The organic layer was washed with 1N HCl (3x), water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* Crystallization from dichloromethane - ether - hexane afforded the title compound as a yellow solid (132.1 mg, 97.7%). ^1H NMR (MeOD, 400MHz) δ ppm 8.76 (s, 1H), 7.92 (s, 1H), 7.86 (s, 1H), 7.64 (dd, J = 10.13, 1.84 Hz, 1H), 7.55-7.50 (m, 1H), 6.72 (t, J = 8.49 Hz, 1H); LCMS (method D1): R_T = 0.77 min, $[M+H]^+$ = 399.

Step 2: 5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid (2-vinyloxy-ethoxy)-amide

[0329]



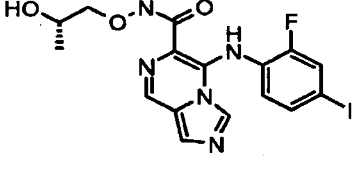
[0330] A mixture of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid (110 mg, 0.28 mmol), *O*-(2-vinyloxy-ethyl)-hydroxylamine (45.6 mg, 0.44 mmol, 1.6 eq.), HATU (157.6 mg, 0.41 mmol, 1.5 eq.), and DIPEA (96.0 μL, 0.55 mmol, 2.0 eq.) in anhydrous DMF (4.2 mL) was stirred for 18 hours under N_2 at ambient temperature. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate followed by water and brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0% to 15%, methanol in dichloromethane) to afford the desired product as a yellow solid (24 mg, 18%). LCMS (method D1): R_T = 1.00 min, $[M+H]^+$ = 484.

Step 3: 5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid (2-hydroxy-ethoxy)-amide

[0331] To a solution of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid (2-vinyloxy-ethoxy)-amide (24.0 mg, 0.05 mmol) in methanol (0.5 mL) and dichloromethane (1.0mL) was added 4M HCl in 1,4-dioxane (30 μL, 0.1 mmol, 2.5 eq.), and the reaction was stirred at ambient temperature under N_2 for 2h. The reaction mixture was concentrated *in vacuo* then poured into ethyl acetate. The organic layer was washed with a saturated solution of sodium bicarbonate, water, and brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0% to 25%, methanol in dichloromethane) to afford the title compound as yellow solid (11.6 mg, 51 %). ^1H NMR (MeOD, 400MHz) δ ppm 8.74 (s, 1H), 7.87 (s, 1H), 7.84 (s, 1H), 7.62 (dd, J = 10.20, 1.82 Hz, 1H), 7.48 (d, J = 8.41 Hz, 1H), 6.61 (t, J = 8.53 Hz, 1H), 4.05 (t, J = 4.80 Hz, 2H), 3.78 (t, J = 4.80Hz, 2H)); LCMS (method E1): R_T = 4.33 min, $[M+H]^+$ = 458.

EXAMPLE 16: 5-(2-Fluoro-4-iodo-phenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide

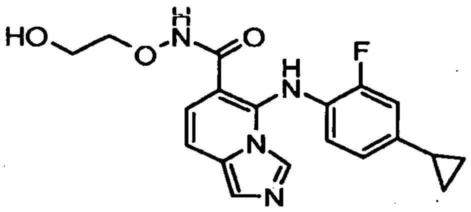
[0332]



[0333] To a solution of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid (85 mg, 0.21 mmol) in anhydrous DMF (1.0 mL) was added (S)-1-aminooxy-propan-2-ol hydrochloride (32.7 mg, 0.26 mmol, 1.2 eq.), DIPEA (0.13mL, 0.77 mmol, 3.6 eq.), HOBt (36.0 mg, 0.26 mmol, 1.2 eq.) and EDCI (51.2 mg, 0.26 mmol, 1.2 eq.), and the reaction mixture was stirred at ambient temperature under N_2 for 16 hours. The reaction mixture was poured into ethyl acetate, and the organic layer was washed with a saturated solution of sodium bicarbonate, 50% brine and brine. The organic phase was isolated, dried (Na_2SO_4), filtered and *concentrated in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0% to 40%, methanol in ethyl acetate) to give an oil. Crystallization from dichloromethane - ether - hexane afforded the title compound as a yellow solid (10.7 mg, 10.6 %). ^{1}H NMR (MeOD, 400MHz) δ ppm 8.76 (s, 1H), 7.92 (s, 1H), 7.86 (s, 1H), 7.64 (dd, J = 10.13, 1.84 Hz, 1H), 7.55-7.50 (m, 1H), 6.72 (t, J = 8.49 Hz, 1H); LCMS (method E1): R_T = 5.14 min, $[M+H]^+$ = 472.

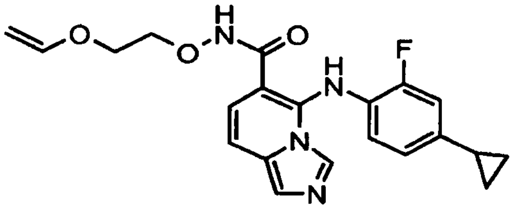
EXAMPLE 17: 5-(4-Cyclopropyl-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide

[0334]



Step 1: 5-(4-Cyclopropyl-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxy-ethoxy)-amide

[0335]



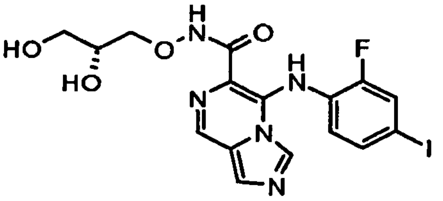
[0336] To a mixture of 5-(4-cyclopropyl-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (400 mg, 1.29 mmol), O-(2-vinyloxyethyl)-hydroxylamine (265 mg, 2.57 mmol) and HOBt (225 mg, 1.67 mmol) in DMF (5 mL) was added EDCI hydrochloride (320 mg, 1.67 mmol), and DIPEA (0.290 mL, 1.67 mmol) before the reaction mixture was stirred at room temperature for 18 hours. The products were partitioned between ethyl acetate and saturated aqueous $NaHCO_3$, the organic layer separated and washed with brine then dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0-35% ethyl acetate in cylcohexane) to give the title compound (270 mg, 53%). LCMS (Method B): R_T 2.79 $[M+H]^+$ 397.

Step 2: 5-(4-Cyclopropyl-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide

[0337] To a solution of 5-(4-cyclopropyl-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-vinyloxy-ethoxy)-amide (270 mg, 0.681 mmol) in methanol (10 mL) was added 1M hydrochloric acid (2 mL, 2 mmoL) and the mixture stirred at room temperature for 2 hours. Solvent was removed *in vacuo,* and then saturated aqueous $NaHCO_3$ added and the mixture extracted with ethyl acetate. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was triturated with TBME and the solid collected by filtration to give the title compound as an off-white solid (103 mg, 41%). LCMS (Method A): R_T 5.68 $[M+H]^+$ 371. ^{1}H NMR (DMSO-d_6, 400MHz) 7.81 (1 H, s), 7.37-7.34 (1 H, m), 7.27 (1 H, d, J = 9.37 Hz), 6.95 (1 H, d, J = 9.34 Hz), 6.91 (1 H, dd, J = 12.49, 1.92 Hz), 6.75 (1 H, dd, J = 8.27, 1.96 Hz), 6.56-6.46 (1 H, m), 3.71-3.65 (2 H, m), 3.48-3.43 (2 H, m), 1.89-1.80 (1 H, m), 0.91-0.85 (2 H, m), 0.65-0.57 (2 H, m).

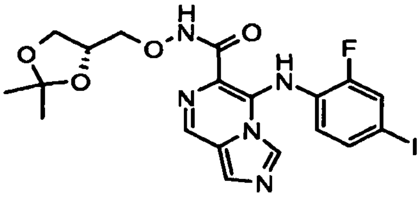
EXAMPLES 18: (R)-*N*-(2,3-Dihydroxypropoxy)-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide

[0338]



Step 1: (R)-*N*-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide

[0339]



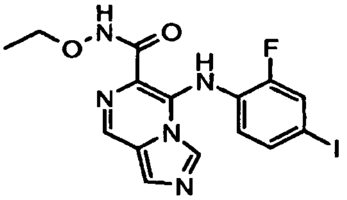
[0340] To a solution of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid (100.0 mg, 0.25 mmol) in anhydrous DMF (2.5 mL) was added, in order, (R)-O-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)hydroxylamine (40.7 mg, 0.28 mmol, 1.1 eq.), HOBt (37.3 mg, 0.27 mmol, 1.1 eq.), EDCI (53.0 mg, 0.27 mmol, 1.1 eq.), and N-methylmorpholine (0.1 mL, 0.91 mmol, 3.6 mmol). The reaction mixture was stirred at room temperature under N_2 for 3 days. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with a saturated solution of sodium bicarbonate, water and brine. The organic phase was isolated, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 80% to 100%, ethyl acetate in hexane, followed by gradient 0 to 20% methanol in ethyl acetate) to give a yellow solid (72.6 mg, 54.8%). LCMS (method D1): R_T = 0.97 min, $[M+H]^+$ = 528.

Step 2: (R)-*N*-(2,3-Dihydroxypropoxy)-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide

[0341] To a heterogeneous mixture of (R)-*N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-a]pyrazine-6-carboxamide (69.5 mg, 0.13 mmol) in anhydrous methanol (1.6 mL) was added 4M HCl in 1,4-dioxane (0.13 mL, 0.5 mmol, 4.0 eq). The reaction mixture was stirred at room temperature for 10 minutes. Solid sodium sulfate (200 mg) was then added. The reaction mixture was absorbed onto silica and then subjected to flash chromatography (Si-PPC, gradient 0% to 40% methanol in dichloromethane) to give the title compound as yellow foam (43.2 mg, 67.3%). ^1H NMR (DMSO-d_6, 400MHz) δ ppm 11.90 (s, 1H), 10.30 (s, 1H), 8.82 (s, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.74 (d, J = 9.6 Hz, 1H), 7.44 (d, 8.4 Hz, 1H), 6.60 (t, J = 8.4 Hz, 1H), 4.86 (d, J = 4.4 Hz, 1H), 4.55 (broad s, 1H), 3.99-3.91 (m, 1H), 3.79-3.69 (m, 2H), 3.39 (broad s, 2H); LCMS (method E2): R_T = 8.40 min, $[M+H]^+$ = 488.

EXAMPLE 19: *N*-Ethoxy-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide

[0342]

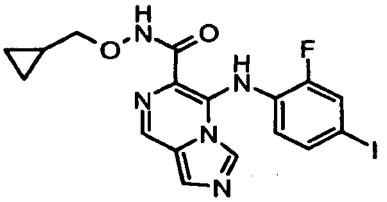


[0343] To a solution of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid methyl ester (165.0 mg, 0.40 mmol) and O-ethylhydroxylamine hydrochloride (78.1 mg, 0.80 mmol, 2.0 eq) in anhydrous THF (9.4 mL) at 0 °C was added lithium hexamethyldisilazide (1M in THF, 1.2 mL, 1.2 mmol, 3.0 eq). After stirring at room temperature for 16h, additional O-ethylhydroxylamine hydrochloride (234.3 mg, 2.40 mmol, 3.0 eq) and lithium hexamethyldisilazide

(1M in THF, 3.6 mL, 3.6 mmol, 9.0 eq) were added at 0 °C, and the reaction mixture was stirred at room temperature for 3 days. The reaction mixture was then quenched with saturated aqueous solution of sodium bicarbonate (5 mL) and diluted with ethyl acetate (50 mL). The organic layer was isolated and washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 45% to 100%, ethyl acetate in hexane, followed by gradient 0 to 15% methanol in ethyl acetate) to give an oil. Crystallization from DCM - ether - hexane afforded the title compound as a yellow solid (33.7 mg, 19.1%). ^{1}H NMR (DMSO-d_6, 400MHz) δ ppm 11.86 (s, 1H), 10.38 (s, 1H), 8.82 (s, 1H), 7.94 (s, 1H), 7.92 (s, 1H), 7.73 (d, J = 10.4 Hz, 1H), 7.44 (d, 8.4 Hz, 1H), 6.57 (t, J = 8.4 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 1.18 (t, J = 6.8 Hz, 3H); LCMS (method D2): R_T = 1.24 min, $[M+H]^+$ = 442.

EXAMPLE 20: *N*-(Cyclopropylmethoxy)-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide

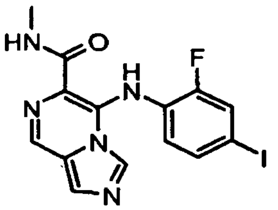
[0344]



[0345] The title compound was prepared in an analogous fashion to *N*-ethoxy-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide, using *O*-(cyclopropylmethyl)-hydroxylamine hydrochloride as the starting material. ^{1}H NMR (DMSO-d_6, 400MHz) δ ppm 11.82 (s, 1H), 10.36 (s, 1H), 8.82 (s, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.73 (dd, J = 10.4 Hz, 1.8 Hz, 1H), 7.44 (d, 8.4 Hz, 1H), 6.58 (t, J = 8.4 Hz, 1H), 3.67 (d, J = 7.2 Hz, 2H), 1.12 to 1.01 (m, 1H), 0.54-0.48 (m, 2H), 0.28-0.23 (m, 2H); LCMS (method D2): R_T = 1.33 min, $[M+H]^+$ = 468.

EXAMPLE 21: 5-(2-Fluoro-4-iodophenylamino)-*N*-methylimidazo[1,5-*a*]pyrazine-6-carboxamide

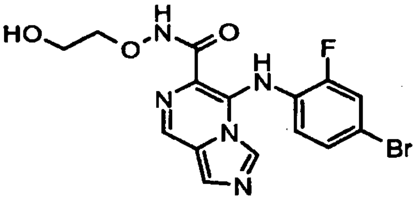
[0346]



[0347] To a solution of 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid methyl ester (108 mg, 0.26 mmol) in anhydrous methanol (0.5 mL) was added 2M methylamine in THF (1.3 mL, 2.6 mmol, 10 eq), and the reaction mixture was stirred at room temperature under N_2 for 3 days. The reaction mixture was diluted with ethyl acetate (50 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to reverse-phase preparative HPLC [Gemini-NX (100x 30mm, 10micron), 0.1% FA in water/ acetonitrile, 5-85%, ramp time in 10 minutes, flow at 60ml/min] to afford the title compound as a white solid (48.3 mg, 44.8%). ^{1}H NMR (DMSO-d_6, 400MHz) δ ppm 10.89 (s, 1H), 8.95 to 8.91 (m, 1H), 8.86 (s, 1H), 7.92 (s, 1H), 7.88 (s, 1H), 7.76 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.44 (d, J = 6.8 Hz, 1H), 6.51 (t, J = 6.8 Hz, 1H), 2.81 (d, 4.0 Hz, 3H); LCMS (method E2): R_T = 12.23 min, $[M+H]^+$ = 412.

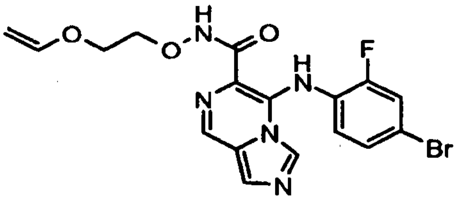
EXAMPLE 22: 5-(4-Bromo-2-fluorophenylamino)-*N*-(2-hydroxy-ethoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide

[0348]



Step 1: 5-(4-Bromo-2-fluorophenylamino)-*N*-(2-(vinyloxy)ethoxy)-imidazo[1,5-*a*]pyrazine-6-carboxamide

[0349]



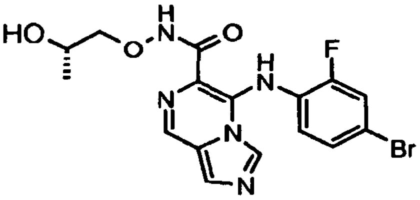
[0350] To a stirred solution of 5-(4-bromo-2-fluoro-phenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid methyl ester (150 mg, 0.41 mmol) and *O*-(2-vinyloxy-ethyl)hydroxylamine (127 mg, 1.23 mmol, 3.0 eq) in anhydrous THF (7.5 mL) at 0 °C was added lithium hexamethyldisilazide (1M in THF, 1.2 mL, 1.23 mmol, 3.0 eq.), and the reaction mixture was stirred at room temperature. After 1h the reaction mixture was quenched with saturated aqueous solution of sodium bicarbonate and diluted with ethyl acetate. The organic layer was isolated and washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0 to 5% methanol in dichoromethane) to give an oil. Crystallization from DCM - ether - hexane afforded the desired product as a pale orange solid (160.2 mg, 89.4%). LCMS (method C): R_T = 2.53 min, $[M+H]^+$ = 437 / 439.

Step 2: 5-(4-Bromo-2-fluorophenylamino)-*N*-(2-hydroxy-ethoxy)-imidazo[1,5-*a*]pyrazine-6-carboxamide

[0351] A solution of 5-(4-bromo-2-fluorophenylamino)-*N*-(2-(vinyloxy)ethoxy)-imidazo[1,5-*a*]pyrazine-6-carboxamide (150 mg, 0.34 mmol) in methanol (4.5 mL) and dichloromethane (8.9 mL) was added 4M HCl in 1,4-dioxane (0.13 mL, 0.5 mmol, 1.5 eq.), and the reaction mixture was stirred at ambient temperature under N_2 for 1h. Solid sodium carbonate (50 mg) was added to the reaction mixture. The reaction mixture was absorbed onto silica and then subjected to flash chromatography (Si-PPC, gradient 0% to 15%, methanol in dichloromethane) to afford the title compound as a white solid. (112.1 mg, 79.5 %). ^1H NMR (DMSO-d_6, 400MHz) δ ppm 11.85 (broad s, 1H), 10.32 (broad s, 1H), 8.83 (s, 1H), 7.97 (s, 1H), 7.92 (s, 1H), 7.64 (dd, J = 10.4 Hz, 2.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 6.77 (t, J = 8.8 Hz, 1H), 4.68 (t, J = 5.6 Hz, 1H), 3.89 (t, 4.8 Hz, 2H), 3.59 (q, J = 5.4 Hz, 2H); LCMS (method D1): R_T = 0.786 min, $[M+H]^+$ = 410 / 412.

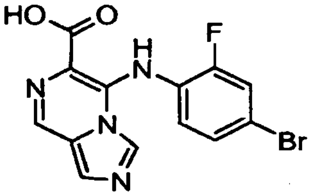
EXAMPLE 23: (S)-5-(4-Bromo-2-fluorophenylamino)-*N*-(2-hydroxy-propoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide

[0352]



Step 1: 5-(4-Bromo-2-fluorophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxylic acid

[0353]



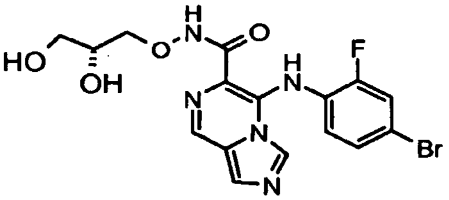
[0354] The desired compound was prepared in an analogous fashion to 5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid, using 5-(4-bromo-2-fluorophenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid methyl ester as the starting material. LCMS (method D1): R_T = 0.713 min, $[M+H]^+$ = 351 / 353.

Step 2: (S)-5-(4-Bromo-2-fluorophenylamino)-*N*-(2-hydroxypropoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide

[0355] To a solution of 5-(4-bromo-2-fluorophenylamino)imidazo[1,5-*a*]-pyrazine-6-carboxylic acid (100 mg, 0.28 mmol) in anhydrous DMF (1.5 mL) was added, in order, (S)-1-aminooxy-propan-2-ol hydrochloride (37.4 mg, 0.29 mmol, 1.03 eq.), HOBt (40.4 mg, 0.30 mmol, 1.05 eq.), EDCI (57.3 mg, 0.30 mmol, 1.05 eq.), and 4-methylmorpholine (0.15 mL, 1.36 mmol, 4.8 eq.). The reaction mixture was stirred at room temperature under N_2 for 7h and then diluted with ether (25 mL) and ethyl acetate (25 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The resultant residue was subjected to flash chromatography (Si-PPC, gradient 0 to 40% methanol in ethyl acetate) to give an oil. Crystallization from DCM - ether - hexane afforded the desired product as a white solid (30.3 mg, 25.0%). ^{1}H NMR (DMSO-d_6, 400MHz) δ ppm 11.88 (broad s, 1H), 10.29 (broad s, 1H), 8.82 (s, 1H), 7.98 (s, 1H), 7.92 (s, 1H), 7.65 (dd, J = 10.6 Hz, 2.2 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 6.78 (t, J = 8.4 Hz, 1H), 4.80 (d, J = 4.0 Hz, 1H), 3.90-3.81 (m, 1H), 3.75-3.62 (m, 2H), 1.05 (d, J = 6.4 Hz, 3H); LCMS (method D2): R_T = 1.516 min, $[M+H]^+$ = 424 / 426.

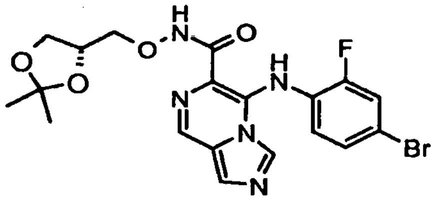
EXAMPLE 24: (R)-5-(4-Bromo-2-fluorophenylamino)-*N*-(2,3-dihydroxypropoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide

[0356]



Step 1: (R)-5-(4-Bromo-2-fluorophenylamino)-*N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide

[0357]



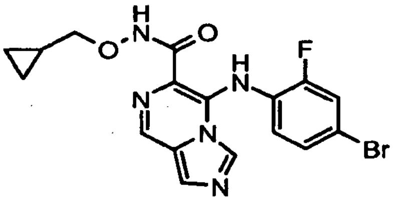
[0358] The desired compound was prepared in an analogous fashion to 5-(4-bromo-2-fluorophenylamino)-*N*-(2-(vinyloxy)ethoxy)-imidazo[1,5-*a*]pyrazine-6-carboxamide, using (R)-*O*-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)hydroxylamine as the starting material. LCMS (method D1): R_T = 0.954 min, $[M+H]^+$ = 480 / 482.

Step 2: 5-(4-Bromo-2-fluorophenylamino)-*N*-(2-hydroxy-ethoxy)-imidazo[1,5-*a*]pyrazine-6-carboxamide

[0359] The desired compound was prepared in an analogous fashion to 5-(4-bromo-2-fluorophenylamino)-*N*-(2-hydroxy-ethoxy)-imidazo[1,5-*a*]pyrazine-6-carboxamide, using (R)-5-(4-bromo-2-fluorophenylamino)-*N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide as the starting material. ^{1}H NMR (DMSO-d_6, 400MHz) δ ppm 11.90 (broad s, 1H), 10.38 (broad s, 1H), 8.81 (s, 1H), 7.96 (s, 1H), 7.91 (s, 1H), 7.65 (d, J = 10.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 6.77 (t, J = 8.8 Hz, 1H), 4.87 (s, 1H), 4.56 (broad s, 1H), 3.93 (dd, J = 9.6 Hz, 3.2 Hz, 1H), 3.79-3.69 (m, 2H), 3.43-3.35 (m, 2H); LCMS (method D1): R_T = 0.724 min, $[M+H]^+$ = 440 / 442.

EXAMPLE 25: 5-(4-Bromo-2-fluorophenylamino)-*N*-(cyclopropylmethoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide

[0360]



[0361] The title compound was prepared in an analogous fashion to *N*-(cyclopropylmethoxy)-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide, using 5-(4-bromo-2-fluoro-phenylamino)-imidazo[1,5-*a*]pyrazine-6-carboxylic acid methyl ester as the starting material. ^{1}H NMR (MeOD, 400MHz) δ ppm 8.74 (s, 1H), 7.87 (s, 1H), 7.84 (s, 1H), 7.48 (dd, J = 10.4 Hz, 3.2 Hz, 1H), 7.30 (d, 8.4 Hz, 1H), 6.75 (t, J = 8.4 Hz, 1H), 3.79 (d, J = 7.2 Hz, 2H), 1.26-1.13 (m, 1H), 0.62-0.55 (m, 2H), 0.36 to 0.30 (m, 2H); LCMS (method D1): R_T = 0.985 min, $[M+H]^+$ = 420 / 422.

Claims

1. A compound for use in a method for the treatment of cancer which is selected from:

   5-(2-fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxyethoxy)-amide;
   5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((R)-2,3-dihydroxy-propoxy)-amide;
   5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide;
   5-(4-bromo-2-fluorophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxyethoxy)-amide;
   5-(4-bromo-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide;
   5-(4-bromo-2-fluoro-phenylamino)-8-fluoro-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide;
   8-fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide;
   8-fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((R)-2,3-dihydroxy-propoxy)-amide;
   8-fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide;
   5-(2-fluoro-methanesulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide;
   5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid (2-hydroxy-ethoxy)-amide;
   5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide;
   5-(4-cyclopropyl-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide;
   (R)-*N*-(2,3-dihydroxypropoxy)-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide;
   N-ethoxy-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide;
   N-(cyclopropylmethoxy)-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide;
   5-(2-fluoro-4-iodophenylamino)-*N*-methylimidazo[1,5-*a*]pyrazine-6-carboxamide;
   5-(4-bromo-2-fluorophenylamino)-*N*-(2-hydroxy-ethoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide;
   (S)-5-(4-bromo-2-fluorophenylamino)-*N*-(2-hydroxy-propoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide;
   (R)-5-(4-bromo-2-fluorophenylamino)-*N*-(2,3-dihydroxy-propoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide; and,
   5-(4-bromo-2-fluorophenylamino)-*N*-(cyclopropyl-methoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide; or a pharmaceutically acceptable salt thereof;
   the method comprising administering the compound in combination with gemcitabine or a taxoid.

2. The compound for use in a method for the treatment of cancer according to claim 1, wherein the compound is 5-(2-fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxyethoxy)-amide, or a pharmaceutical-

ly acceptable salt thereof.

3. The compound for use in a method for the treatment of cancer according to claim 1 or claim 2, wherein the cancer is pancreatic cancer, non-small cell lung cancer, colorectal cancer, endometrial cancer, ovarian cancer or malignant melanoma.

4. The compound for use in a method for the treatment of cancer according to one one of claims 1 to 3, wherein the compound is administered simultaneously with the taxoid or gemcitabine.

5. The compound for use in a method for the treatment of cancer according to one one of claims 1 to 3, wherein the compound is administered sequentially to the taxoid or gemcitabine.

6. The compound for use in a method for the treatment of cancer according to one one of claims 1 to 3, wherein the compound is administered separately from to the taxoid or gemcitabine.

7. The compound for use in a method for the treatment of cancer according to any one of the preceding claims, wherein the taxoid is paclitaxel.

8. The compound for use in a method for the treatment of cancer according to any one of the preceding claims, wherein the treatment is for oral adminstration.

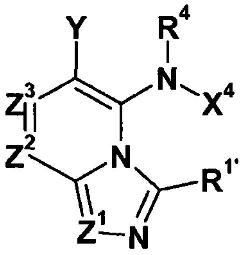
9. The compound for use in a method for the treatment of cancer according to any one of claims 1 to 3, wherein the compound is for administration in combination with gemcitabine for the treatment of pancreatic cancer.

10. The compound for use in a method for the treatment of cancer according to any one of claims 1 to 3, wherein the compound is for administration in combination with paclitaxel for the treatment of non-small cell lung cancer or ovarian cancer.

11. A compound for use in a method for the treatment of cancer or an inflammatory disorder **characterised by** mutation or overexpression of MEK kinase, wherein the compound is selected from:

5-(2-fluoro-4-iodophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxyethoxy)-amide;
5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((R)-2,3-dihydroxy-propoxy)-amide;
5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide;
5-(4-bromo-2-fluorophenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxyethoxy)-amide;
5-(4-bromo-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide;
5-(4-bromo-2-fluoro-phenylamino)-8-fluoro-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide;
8-fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide;
8-fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((R)-2,3-dihydroxy-propoxy)-amide;
8-fluoro-5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide;
5-(2-fluoro-methanesulfanyl-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide;
5-(2-fluoro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid (2-hydroxy-ethoxy)-amide;
5-(2-flu.oro-4-iodo-phenylamino)-imidazo[1,5-a]pyrazine-6-carboxylic acid ((S)-2-hydroxy-propoxy)-amide;
5-(4-cyclopropyl-2-fluoro-phenylamino)-imidazo[1,5-a]pyridine-6-carboxylic acid (2-hydroxy-ethoxy)-amide;
(R)-*N*-(2,3-dihydroxypropoxy)-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-a]pyrazine-6-carboxamide;
N-ethoxy-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide;
N-(cyclopropylmethoxy)-5-(2-fluoro-4-iodophenylamino)imidazo[1,5-*a*]pyrazine-6-carboxamide;
5-(2-fluoro-4-iodophenylamino)-*N*-methylimidazo[1,5-*a*]pyrazine-6-carboxamide;
5-(4-bromo-2-fluorophenylamino)-*N*-(2-hydroxy-ethoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide;
(S)-5-(4-bromo-2-fluorophenylamino)-*N*-(2-hydroxy-propoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide;
(R)-5-(4-bromo-2-fluorophenylamino)-*N*-(2,3-dihydroxy-propoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide; and,
5-(4-bromo-2-fluorophenylamino)-*N*-(cyclopropyl-methoxy)imidazo[1,5-*a*]pyrazine-6-carboxamide; or a pharmaceutically acceptable salt thereof.

12. A compound represented by Formula 1, and salts thereof, for use in a method for the treament of an inflammatory disorder:



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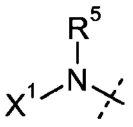
wherein:

Z^1 is CR^1 or N;
R^1 is H, C_1-C_3 alkyl, halo, CF_3, CHF_2, CN, OR^A or NR^AR^A;
$R^{1'}$ is H, C_1-C_3 alkyl, halo, CF_3, CHF_2, CN, OR^A, or NR^AR^A;
wherein each R^A is independently H or C_1-C_3 alkyl;
Z^2 is CR^2 or N;
Z^3 is CR^3 or N; provided that only one of Z^1, Z^2 and Z^3 can be N at the same time;
R^2 and R^3 are independently selected from H, halo, CN, CF_3, $-OCF_3$, $-NO_2$, $-(CR^{14}R^{15})_nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{11}R^{12}$, $-(CR^{14}R^{15})_nOR^{11}$, $-(CR^{14}R^{15})_nSR^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')R^{11}$ $-(CR^{14}R^{15})_nNR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_nNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nOC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_nOP(=Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_n$ $S(O)_2NR^{11}R^{12}$, $-(CR^{14}R^{15})_nS(O)(OR^{11})$, $-(CR^{14}R^{15})_nS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_n$ $SC(=Y')R^{11}$, $-(CR^{14}R^{15})_nSC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nSC(=Y')NR^{11}R^{12}$, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl;
R^4 is H, C_1-C_6 alkyl or C_3-C_4 carbocyclyl;
Y is W-C(O)- or W';
Wis



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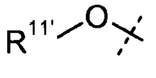


;

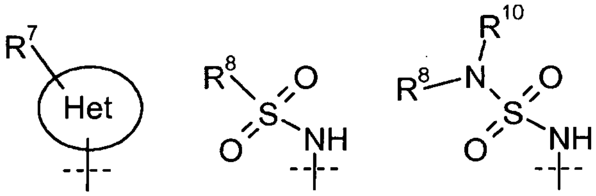
R^5 is H or C_1-C_{12} alkyl;
X^1 is selected from $R^{11'}$ and $-OR^{11'}$; when X^1 is $R^{11'}$, X^1 is optionally taken together with R^5 and the nitrogen atom to which they are bound to form a 4-7 membered saturated or unsaturated ring having 0-2 additional heteroatoms selected from O, S and N, wherein said ring is optionally substituted with one or more groups selected from halo, CN, CF_3, $-OCF_3$, $-NO_2$, oxo, $-(CR^{19}R^{20})_nC(=Y')R^{16}$, $-(CR^{19}R^{20})_n$ $C(=Y')OR^{16}$, $-(CR^{19}R^{20})_nC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_n$-SR^{16}, $-(CR^{19}R^{20})_nNR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_n$ $NR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_n$ $NR^{18}C(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{17}SO_2R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nS(O)R^{16}$, $-(CR^{19}R^{21})_nS(O)_2R^{16}$, $-(CR^{19}R^{20})_nS(O)_2NR^{16}R^{17}$, $-(CR^{19}R^{20})_nS(O)(OR^{16})$, $-(CR^{19}R^{20})_n$ $S(O)_2(OR^{16})$, $-(CR^{19}R^{20})_n$ $SC(=Y')R^{16}$, $-(CR^{19}R^{20})_n$ $SC(=Y')OR^{16}$, $-(CR^{19}R^{20})_n$ $SC(=Y')NR^{16}R^{17}$, and R^{21};
each $R^{11'}$ is independently H, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl;

R^{11}, R^{12} and R^{13} are independently H, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl,

or R^{11} and R^{12} together with the nitrogen to which they are attached form a 3-8 membered saturated, unsaturated or aromatic ring having 0-2 heteroatoms selected from O, S and N, wherein said ring is optionally substituted with one or more groups selected from halo, CN, CF_3, $-OCF_3$, $-NO_2$, C_1-C_6 alkyl, -OH, -SH, $-O(C_1$-C_6 alkyl), $-S(C_1$-C_6 alkyl), $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl$)_2$, $-SO_2(C_1$-C_6 alkyl), $-CO_2H$, $-CO_2(C_1$-C_6 alkyl), $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl), $-C(O)N(C_1$-C_6 alkyl$)_2$, $-N(C_1$-C_6 alkyl$)C(O)(C_1$-C_6 alkyl), $-NHC(O)(C_1$-C_6 alkyl), $-NHSO(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl$)SO_2(C_1$-C_6 alkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-C_6 alkyl), $-SO_2N(C_1$-C_6 alkyl$)_2$, $-OC(O)NH_2$, $-OC(O)NH(C_1$-C_6 alkyl), $-OC(O)N(C_1$-C_6 alkyl$)_2$, $-OC(O)O(C_1$-C_6 alkyl), $-NHC(O)NH(C_1$-C_6 alkyl), $-NHC(O)N(C_1$-C_6 alkyl$)_2$, $-N(C_1$-C_6 alkyl$)C(O)NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl$)C(O)N(C_1$-C_6 alkyl$)_2$, $-NHC(O)NH(C_1$-C_6 alkyl), $-NHC(O)N(C_1$-C_6 alkyl$)_2$, $-NHC(O)O(C_1$-C_6 alkyl), and $-N(C_1$-C_6 alkyl$)C(O)O(C_1$-C_6 alkyl);

R^{14} and R^{15} are independently selected from H, C_1-C_{12} alkyl, aryl, carbocyclyl, heterocyclyl, and heteroaryl;

W' is



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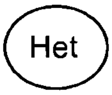
wherein



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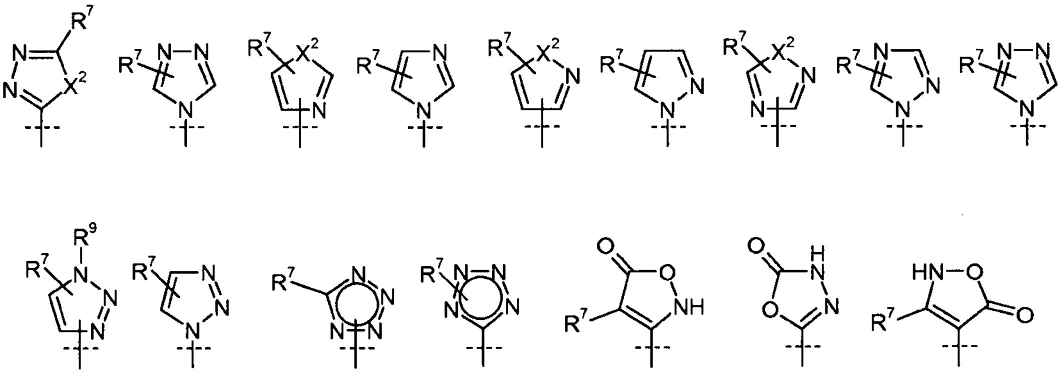


each X^2 is independently O, S, or NR^9;

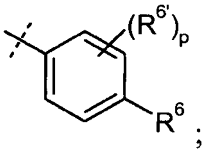
each R^7 is independently selected from H, halo, CN, CF_3, $-OCF_3$, $-NO_2$, $-(CR^{14}R^{15})_nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR14R^{15})_nC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{11}R^{12}$, $-(CR^{14}R^{15})_nOR^{11}$, $-(CR^{14}R^{15})_nSR^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')R^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_nNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nOC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_nOP(=Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_nS(O)_2NR^{11}R^{12}$, $-(CR^{14}R^{15})_nS(O)(OR^{11})$, $-(CR^{14}R^{15})_nS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_n$ $SC(=Y')R^{11}$, $-(CR^{14}R^{15})_nSC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nSC(=Y')NR^{11}R^{12}$, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl;

each R^8 is independently selected from C_1-C_{12} alkyl, aryl, carbocyclyl, heterocyclyl, and heteroaryl;

R^9 is selected from H, $-(CR^{14}R^{15})_nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_qNR^{11}R^{12}$, $-(CR^{14}R^{15})_qOR^{11}$, $-(CR^{14}R^{15})_qSR^{11}$, $-(CR^{14}R^{15})_qNR^{12}C(=Y')R^{11}$, $-(CR^{14}R^{15})_qNR^{12}C(=Y)OR^{11}$, $-(CR^{14}R^{15})_qNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_qNR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_qOC(=Y')R^{11}$, $-(CR^{14}R^{15})_qOC(=Y')OR^{11}$, $-(CR^{14}R^{15})_qOC(=Y')NR^{11}R^{12}$, $(CR^{14}R^{15})_qOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_qOP(-Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_qOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_n\ S(O)_2NR^{11}R^{12}$, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl;

R^{10} is H, C_1-C_6 alkyl or C_3-C_4 carbocyclyl;

X^4 is



;

R^6 is H, halo, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heteroaryl, heterocyclyl, $-OCF_3$, $-NO_2$, $-Si(C_1$-C_6 alkyl), $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, or $-(CR^{19}R^{20})_n-SR^{16}$;

$R^{6'}$ is H, halo, C_1-C_6 alkyl, carbocyclyl, CF_3, $-OCF_3$, $-NO_2$, $-Si(C_1$-C_6 alkyl), $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_n-SR^{16}$, C_2-C_8 alkenyl, C_2-C_8 alkynyl, heterocyclyl, aryl, or heteroaryl;

p is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

q is 2 or 3;

wherein each said alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl of R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, R^8, R^9, R^{10}, R^{11}, $R^{11'}$, R^{12}, R^{13}, R^{14}, R^{15} and R^A is independently optionally substituted with one or more groups independently selected from halo, CN, CF_3, $-OCF_3$, $-NO_2$, oxo, $-Si(C_1$-C_6 alkyl), $-(CR^{19}R^{20})_nC(=Y')R^{16}$, $-(CR^{19}R^{20})_n\ C(=Y')OR^{16}$, $-(CR^{19}R^{20})_nC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_nSR^{16}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_nNR^{18}C(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{17}SO_2R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, $(CR^{19}R^{20})_nOS(O)_2(OR^{16})$,-$(CR^{19}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nS(O)R^{16}$, $-(CR^{19}R^{20})_nS(O)_2R^{16}$, $-(CR^{19}R^{20})_nS(O)_2NR^{16}R^{17}$, $-(CR^{19}R^{20})_nS(O)(OR^{16})$, $-(CR^{19}R^{20})_n\ S(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nSC(=Y')R^{16}$, $-(CR^{19}R^{20})_nSC(=Y')OR^{16}$, $-(CR^{19}R^{20})_n\ SC(=Y')NR^{16}R^{17}$, and R^{21};

each R^{16}, R^{17} and R^{18} is independently H, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein said alkyl, alkenyl, alkynyl,carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more groups selected from halo, CN, $-OCF_3$, CF_3, $-NO_2$, C_1-C_6 alkyl, -OH, -SH, $-O(C_1$-C_6 alkyl), $-S(C_1$-C_6 alkyl), $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl$)_2$, $-SO_2(C_1$-C_6 alkyl), $-CO_2H$, $-CO_2(C_1$-C_6 alkyl), $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl), $-C(O)N(C_1$-C_6 alkyl$)_2$, $-N(C_1$-C_6 alkyl)$C(O)(C_1$-C_6 alkyl), $-NHC(O)(C_1$-C_6 alkyl), $-NHSO_2(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$SO_2(C_1$-C_6 alkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-C_6 alkyl), $-SO_2N(C_1$-C_6 alkyl$)_2$, -OC(O)NHz, $-OC(O)NH(C_1$-C_6 alkyl), $-OC(O)N(C_1$-C_6 alkyl$)_2$, $-OC(O)O(C_1$-C_6 alkyl), $-NHC(O)NH(C_1$-C_6 alkyl), $-NHC(O)N(C_1$-C_6 alkyl$)_2$, $-N(C_1$-C_6 alkyl)$C(O)NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$C(O)N(C_1$-C_6 alkyl$)_2$, $-NHC(O)NH(C_1$-C_6 alkyl), $-NHC(O)N(C_1$-C_6 alkyl$)_2$, $-NHC(O)O(C_1$-C_6 alkyl), and $-N(C_1$-C_6 alkyl)$C(O)O(C_1$-C_6 alkyl);

or R^{16} and R^{17} together with the nitrogen to which they are attached form a 3-8 membered saturated, unsaturated or aromatic ring having 0-2 heteroatoms selected from O, S and N, wherein said ring is optionally substituted with one or more groups selected from halo, CN, $-OCF_3$, CF_3, $-NO_2$, C_1-C_6 alkyl, -OH, -SH, $-O(C_1$-C_6 alkyl), $-S(C_1$-C_6 alkyl), $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl$)_2$, $-SO_2(C_1$-C_6 alkyl), $-CO_2H$, $-CO_2(C_1$-C_6 alkyl), $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl), $-C(O)N(C_1$-C_6 alkyl$)_2$, $-N(C_1$-C_6 alkyl)$C(O)(C_1$-C_6 alkyl), $-NHC(O)(C_1$-C_6 alkyl), $-NHSO_2(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$SO_2(C_1$-C_6 alkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-C_6 alkyl), $-SO_2N(C_1$-C_6 alkyl$)_2$, $-OC(O)NH_2$, $-OC(O)NH(C_1$-C_6 alkyl), $-OC(O)N(C_1$-C_6 alkyl$)_2$, $-OC(O)O(C_1$-C_6 alkyl), $-NHC(O)NH(C_1$-C_6 alkyl), $-NHC(O)N(C_1$-C_6 alkyl$)_2$, $-N(C_1$-C_6 alkyl)$C(O)NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$C(O)N(C_1$-C_6 alkyl$)_2$, $-NHC(O)NH(C_1$-C_6 alkyl), $-NHC(O)N(C_1$-C_6 alkyl$)_2$, $-NHC(O)O(C_1$-C_6 alkyl), and $-N(C_1$-C_6 alkyl)$C(O)O(C_1$-C_6 alkyl);

R^{19} and R^{20} are independently selected from H, C_1-C_{12} alkyl, $-(CH_2)_n$-aryl,- $(CH_2)_n$-carbocyclyl, $-(CH_2)_n$-heterocyclyl, and $-(CH_2)_n$-heteroaryl;

R^{21} is C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each member of R^{21} is optionally substituted with one or more groups selected from halo, oxo, CN, $-OCF_3$, CF_3,

-NO_2, C_1-C_6 alkyl, -OH, -SH, -O(C_1-C_6 alkyl), -S(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -SO_2(C_1-C_6 alkyl), -CO_2H, -CO_2(C_1-C_6 alkyl), -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -$NHSO_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)SO_2(C_1-C_6 alkyl), -SO_2NH_2, -SO_2NH(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)$_2$, -OC(O)NH_2, -OC(O)NH(C_1-C_6 alkyl), -OC(O)N(C_1-C_6 alkyl)$_2$, -OC(O)O(C_1-C_6 alkyl), -NHC(O)NH(C_1-C_6 alkyl), -NHC(O)N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)C(O)NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)N(C_1-C_6 alkyl)$_2$, -NHC(O)NH(C_1-C_6 alkyl), -NHC(O)N(C_1-C_6 alkyl)$_2$, -NHC(O)O(C_1-C_6 alkyl), and -N(C_1-C_6 alkyl)C(O)O(C_1-C_6 alkyl);
each Y' is independently O, NR^{22}, or S; and
R^{22} is H or C_1-C_{12} alkyl.

Patentansprüche

1. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs, die aus den folgenden ausgewählt ist:

    5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-(2-hydroxyethoxy)amid;
    5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-((R)-2,3-dihydroxypropoxy)amid;
    5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-((S)-2-hydroxypropoxy)amid;
    5-(4-Brom-2-fluorphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-(2-hydroxyethoxy)amid;
    5-(4-Brom-2-fluorphenylamino)-imidazo[1,5-a]pyridin-6-carbonsäure-((S)-2-hydroxypropoxy)amid;
    5-(4-Brom-2-fluorphenylamino)-8-fluorimidazo[1,5-a]pyridin-6-carbonsäure-((S)-2-hydroxypropoxy)amid;
    8-Fluor-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-(2-hydroxyethoxy)amid;
    8-Fluor-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-((R)-2,3-dihydroxypropoxy)amid;
    8-Fluor-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-((S)-2-hydroxypropoxy)amid;
    5-(2-Fluormethansulfanylphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-(2-hydroxyethoxy)amid;
    5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]pyrazin-6-carbonsäure-(2-hydroxyethoxy)amid;
    5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]pyrazin-6-carbonsäure-((S)-2-hydroxypropoxy)amid;
    5-(4-Cyclopropyl-2-fluorphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-(2-hydroxyethoxy)amid;
    (R)-N-(2,3-Dihydroxypropoxy)-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]-pyrazin-6-carboxamid;
    N-Ethoxy-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]pyrazin-6-carboxamid;
    N-(Cyclopropylmethoxy)-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]pyrazin-6-carboxamid;
    5-(2-Fluor-4-iodphenylamino)-N-methylimidazo[1,5-a]pyrazin-6-carboxamid;
    5-(4-Brom-2-fluorphenylamino)-N-(2-hydroxyethoxy)imidazo[1,5-a]pyrazin-6-carboxamid;
    (S)-5-(4-Brom-2-fluorphenylamino)-N-(2-hydroxypropoxy)imidazo[1,5-a]-pyrazin-6-carboxamid;
    (R)-5-(4-Brom-2-fluorphenylamino)-N-(2,3-dihydroxypropoxy)imidazo[1,5-a]-pyrazin-6-carboxamid; und
    5-(4-Brom-2-fluorphenylamino)-N-(cyclopropylmethoxy)imidazo[1,5-a]pyrazin-6-carboxamid; oder einem pharmazeutisch annehmbaren Salz davon;
    wobei das Verfahren das Verabreichen der Verbindung in Kombination mit Gemcitabin oder einem Taxoid umfasst.

2. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs nach Anspruch 1, worin die Verbindung 5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]-pyridin-6-carbonsäure-(2-hydroxyethoxy)amid oder ein pharmazeutisch annehmbares Salz davon ist.

3. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs nach Anspruch 1 oder Anspruch 2, worin der Krebs Bauchspeicheldrüsenkrebs, nichtkleinzelliger Lungenkrebs, Kolorektalkrebs, Endometriumkrebs, Eierstockkrebs oder malignes Melanom ist.

4. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs nach einem der Ansprüche 1 bis 3, worin die Verbindung gleichzeitig mit dem Taxoid oder Gemcitabin verabreicht wird.

5. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs nach einem der Ansprüche 1 bis 3, worin die Verbindung und das Taxoid oder Gemcitabin nacheinander verabreicht werden.

6. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs nach einem der Ansprüche 1 bis 3, worin die Verbindung getrennt von dem Taxoid oder Gemcitabin verabreicht wird.

7. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs nach einem der vorangegangenen

Ansprüche, worin das Taxoid Paclitaxel ist.

8. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs nach einem der vorangegangenen Ansprüche, worin zur Behandlung eine orale Verabreichung vorgesehen ist.

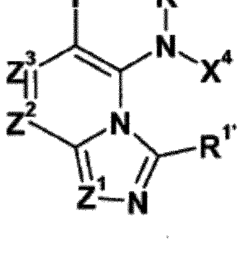
9. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs nach einem der Ansprüche 1 bis 3, worin die Verbindung zur Verabreichung in Kombination mit Gemcitabin zur Behandlung von Bauchspeicheldrüsenkrebs bestimmt ist.

10. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs nach einem der Ansprüche 1 bis 3, worin die Verbindung zur Verabreichung in Kombination mit Paclitaxel zur Behandlung von nichtkleinzelligem Lungenkrebs oder Eierstockkrebs bestimmt ist.

11. Verbindung zur Verwendung in einem Verfahren zur Behandlung von Krebs oder einer durch Mutation oder Überexpression von MEK-Kinase gekennzeichneten Entzündungsstörung, worin die Verbindung aus den folgenden ausgewählt ist:

5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-(2-hydroxy-ethoxy)amid;
5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-((R)-2,3-dihydroxypropoxy)amid;
5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-((S)-2-hydroxypropoxy)amid;
5-(4-Brom-2-fluorphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-(2-hydroxyethoxy)amid;
5-(4-Brom-2-fluorphenylamino)-imidazo[1,5-a]pyridin-6-carbonsäure-((S)-2-hydroxypropoxy)amid;
5-(4-Brom-2-fluorphenylamino)-8-fluorimidazo[1,5-a]pyridin-6-carbonsäure-((S)-2-hydroxypropoxy)amid;
8-Fluor-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-(2-hydroxyethoxy)amid;
8-Fluor-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-((R)-2,3-dihydroxypropoxy)amid;
8-Fluor-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-((S)-2-hydroxypropoxy)amid;
5-(2-Fluormethansulfanylphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-(2-hydroxyethoxy)amid;
5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]pyrazin-6-carbonsäure-(2-hydroxyethoxy)amid;
5-(2-Fluor-4-iodphenylamino)imidazo[1,5-a]pyrazin-6-carbonsäure-((S)-2-hydroxypropoxy)amid;
5-(4-Cyclopropyl-2-fluorphenylamino)imidazo[1,5-a]pyridin-6-carbonsäure-(2-hydroxyethoxy)amid;
(R)-N-(2,3-Dihydroxypropoxy)-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]-pyrazin-6-carboxamid;
N-Ethoxy-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]pyrazin-6-carboxamid;
N-(Cyclopropylmethoxy)-5-(2-fluor-4-iodphenylamino)imidazo[1,5-a]pyrazin-6-carboxamid;
5-(2-Fluor-4-iodphenylamino)-N-methylimidazo[1,5-a]pyrazin-6-carboxamid;
5-(4-Brom-2-fluorphenylamino)-N-(2-hydroxyethoxy)imidazo[1,5-a]pyrazin-6-carboxamid;
(S)-5-(4-Brom-2-fluorphenylamino)-N-(2-hydroxypropoxy)imidazo[1,5-a]-pyrazin-6-carboxamid;
(R)-5-(4-Brom-2-fluorphenylamino)-N-(2,3-dihydroxypropoxy)imidazo[1,5-a]-pyrazin-6-carboxamid; und
5-(4-Brom-2-fluorphenylamino)-N-(cyclopropylmethoxy)imidazo[1,5-a]pyrazin-6-carboxamid; oder einem pharmazeutisch annehmbaren Salz davon.

12. Verbindung, dargestellt durch Formel I, und Salze davon zur Verwendung in einem Verfahren zur Behandlung einer Entzündungsstörung:



I

worin:

Z^1 CR^1 oder N ist;
R^1 H, C_{1-3}-Alkyl, Halogen, CF_3, CHF_2, CN, OR^A oder NR^AR^A ist;
$R^{1'}$ H, C_{1-3}-Alkyl, Halogen, CF_3, CHF_2, CN, OR^A oder NR^AR^A ist;

worin R^A jeweils unabhängig H oder C_{1-3}-Alkyl ist;

Z^2 CR^2 oder N ist;

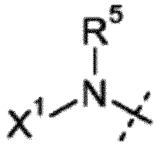
Z^3 CR^3 oder N ist; mit der Maßgabe, dass nur eines von Z^1, Z^2 und Z^3 gleichzeitig N sein kann;

R^2 und R^3 jeweils unabhängig aus H, Halogen, CN, CF_3, $-OCF_3$, $-NO_2$, $-(CR^{14}R^{15})_nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$- $(CR^{14}R^{15})_nC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{11}R^{12}$, $-(CR^{14}R^{15})_nOR^{11}$, $-(CR^{14}R^{15})_nSR^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')R^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_nNR^{13}C(-Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nOC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_nOP(=Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_n S(O)_2NR^{11}R^{12}$, $-(CR^{14}R^{15})_nS(O)(OR^{11})$, $-(CR^{14}R^{15})_nS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_n SC(=Y')R^{11}$, $-(CR^{14}R^{15})_nSC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nSC(=Y')NR^{11}R^{12}$, C_{1-12}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Carbocyclyl, Heterocyclyl, Aryl und Heteroaryl ausgewählt ist;

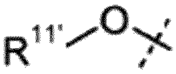
R^4 = H, C_{1-6}-Alkyl oder C_{3-4}-Carbocyclyl ist;

Y = W-C(O)- oder W' ist;

W



oder



ist;

R^5 H oder C_{1-12}-Alkyl ist;

X^1 aus $R^{11'}$ und $-OR^{11'}$ ausgewählt ist; wobei X^1, wenn $X^1 = R^{11'}$ ist, gegebenenfalls zusammen mit R^5 und dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring mit 0 bis 2 zusätzlichen, aus O, S und N ausgewählten Heteroatomen bildet, worin der Ring gegebenenfalls mit einer oder mehreren aus Halogen, CN, CF_3, $-OCF_3$, $-NO_2$, Oxo, $-(CR^{19}R^{20})_nC(=Y')R^{16}$, $-(CR^{19}R^{20})_n C(=Y')OR^{16}$, $-(CR^{19}R^{20})_nC(=Y')NR^{16}R^{11}$, $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_n-SR^{16}$, $-(CR^{19}R^{20})_n NR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_n NR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_n NR^{18}C(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{17}SO_2R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nS(O)R^{16}$, $-(CR^{19}R^{20})_nS(O)_2R^{16}$, $-(CR^{19}R^{20})_nS(O)_2NR^{16}R^{17}$, $(CR^{19}R^{20})_nS(O)(OR^{16})$, $-(CR^{19}R^{20})_n S(O)_2(OR^{16})$, $-(CR^{19}R^{20})_n SC(=Y')R^{16}$, $-(CR^{19}R^{20})_n SC(=Y')OR^{16}$, $-(CR^{19}R^{20})_n SC(=Y')NR^{16}R^{17}$ und R^{21} ausgewählten Gruppen substituiert ist;

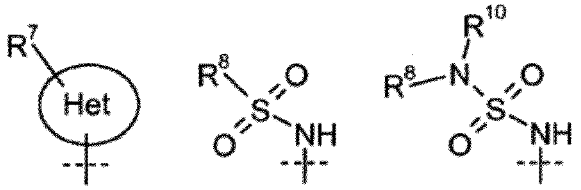
die $R^{11'}$ jeweils unabhängig H, C_{1-12}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Carbocyclyl, Heterocyclyl, Aryl oder Heteroaryl sind;

R^{11}, R^{12} und R^{13} jeweils unabhängig H, C_{1-12}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Carbocyclyl, Heterocyclyl, Aryl oder Heteroaryl ist,

oder R^{11} und R^{12} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 3- bis 8-gliedrigen, gesättigten oder ungesättigten Ring mit 0 bis 2 zusätzlichen, aus O, S und N ausgewählten Heteroatomen bildet, worin der Ring gegebenenfalls mit einer oder mehreren aus Halogen, CN, CF_3, $-OCF_3$, $-NO_2$, C_{1-6}-Alkyl, -OH, -SH, $-O(C_{1-6}$-Alkyl), $-S(C_{1-6}$-Alkyl), $-NH_2$, $-NH(C_{1-6}$-Alkyl), $-N(C_{1-6}$-Alkyl$)_2$, $SO_2(C_{1-6}$-Alkyl), $-CO_2H$, $-CO_2(C_{1-6}$-Alkyl), $-C(O)NH_2$, $-C(O)NH(C_{1-6}$-Alkyl), $-C(O)N(C_{1-6}$-Alkyl$)_2$, $-N(C_{1-6}$-Alkyl)C(O)(C_{1-6}-alkyl), $-NHC(O)(C_{1-6}$-Alkyl), $NHSO_2(C_{1-6}$-Alkyl), $-N(C_{1-6}$-Alkyl)-$SO_2(C_{1-6}$-alkyl), $-SO_2NH_2$, $-SO_2NH(C_{1-6}$-Alkyl), $-SO_2N(C_{1-6}$-Alkyl$)_2$, $-OC(O)NH_2$,
$-O-C(O)NH(C_{1-6}$-Alkyl), $-OC(O)N(C_{1-6}$-Alkyl$)_2$, $-N(C_{1-6}$-Alkyl)C(O)NH(C_{1-6}-alkyl), $-N(C_{1-6}$-Alkyl)C(O)N(C_{1-6}-alkyl$)_2$, $-NHC(O)NH(C_{1-6}$-Alkyl), $-NHC(O)N(C_{1-6}$-Alkyl$)_2$, $-NHC(O)O(C_{1-6}$-Alkyl) und $-N(C_{1-6}$-Alkyl)C(O)O(C_{1-6}-Alkyl) ausgewählten Gruppen substituiert ist;

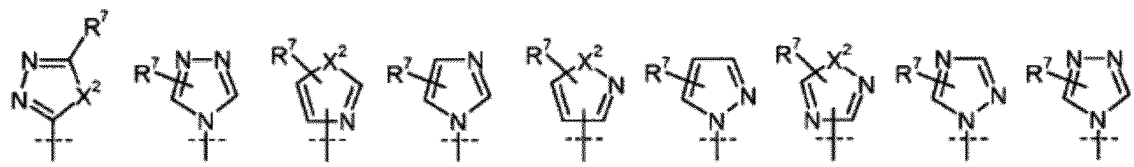
R^{14} und R^{15} jeweils unabhängig aus H, C_{1-12}-Alkyl, Aryl, Carbocyclyl, Heterocyclyl und Heteroaryl ausgewählt sind;

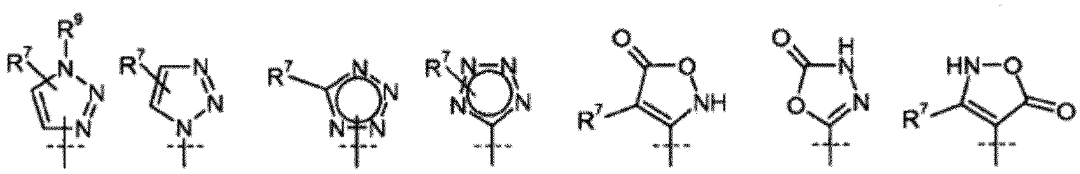
W'



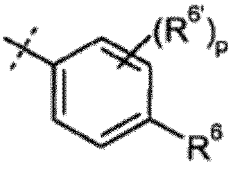
ist;
worin

Folgendes ist:





die X^2 jeweils unabhängig O, S oder NR^9 sind;
die R^7 jeweils unabhängig aus H, Halogen, CN, CF_3, $-OCF_3$, $-NO_2$, $-(CR^{14}R^{15})_nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nC(=Y)NR^{11}R^{12}$, $-(CR^{14}R^{14})_nNR^{11}R^{12}$, $-(CR^{14}R^{15})_nOR^{11}$, $-(CR^{14}R^{15})_nSR^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')R^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_nNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{12}SO_2R^{11}$, $(CR^{14}R^{15})_nOC(=Y')R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')OR^{11}$, $-(CR^{14}R^{14})_nOC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nOS(O)_2(OR^{11})$, $-(CR^{14}R^{11})_nOP(=Y)(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_nS(O)_2NR^{11}R^{12}$, $-(CR^{14}R^{15})_nS(O)(OR^{11})$, $-(CR^{14}R^{15})_nS(O)_2(OR^{11})$, $-(CR^{14}R^{14})_n$ $SC(=Y')R^{11}$, $-(CR^{14}R^{15})_nSC(=Y')R^{11}$,- $(CR^{14}R^{15})_nSC(=Y')NR^{11}R^{12}$, C_{1-12}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Carbocyclyl, Heterocyclyl, Aryl und Heteroaryl ausgewählt sind;
die R^8 jeweils unabhängig aus C_{1-12}-Alkyl, Aryl, Carbocyclyl, Heterocyclyl und Heteroaryl ausgewählt sind;
R^9 aus H, $-(CR^{14}R^{15})_nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_qNR^{11}R^{12}$, $-(CR^{14}R^{15})_qOR^{11}$, $-(CR^{14}R^{15})_qSR^{11}$, $-(CR^{14}R^{13})_qNR^{12}C(=Y')R^{11}$, $-(CR^{14}R^{15})_qNR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_qNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_qNR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_qOC(=Y')R^{11}$, $-(CR^{14}R^{15})_qOC(=Y')OR^{11}$, $-(CR^{14}R^{15})_qOC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_qOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})OP(=Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_qOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_n$ $S(O)_2NR^{11}R^{12}$, C_{1-12}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Carbocyclyl, Heterocyclyl, Aryl und Heteroaryl ausgewählt sind;
R^{10} H, C_{1-6}-Alkyl oder C_{3-4}-Carbocyclyl ist;
X^4



ist;

R^6 H, Halogen, C_{1-6}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Carbocyclyl, Heteroaryl, Heterocyclyl, -OCF_3, -NO_2, -Si(C_{1-6}-Alkyl), -$(CR^{19}R^{20})_nNR^{16}R^{17}$, -$(CR^{19}R^{20})_nOR^{16}$ oder -$(CR^{19}R^{20})_n$-SR^{16} ist;

R^6 H, Halogen, C_{1-6}-Alkyl, Carbocyclyl, CF_3, -OCF_3, -NO_2, -Si(C_{1-6}-Alkyl), -$(CR^{19}R^{20})_nNR^{16}R^{17}$, -$(CR^{19}R^{20})_nOR^{16}$, -$(CR^{19}R^{20})_n$-$SR^{16}$, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Heterocyclyl, Aryl oder Heteroaryl ist;

p = 0, 1, 2 oder 3 ist;

n = 0, 1, 2 oder 3 ist;

q = 2 oder 3 ist;

worin jedes Alkyl, Alkenyl, Alkinyl, Carbocyclyl, Heterocyclyl, Aryl und Hetero-aryl von R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, R^8, R^9, R^{10}, R^{11}, $R^{11'}$, R^{12}, R^{13}, R^{14}, R^{15} und R^A jeweils unabhängig gegebenenfalls mit einer oder mehreren, jeweils unabhängig aus Halogen, CN, CF_3, -OCF_3, -NO_2, Oxo, Si(C_{1-6}-Alkyl),- $(CR^{19}R^{20})_nC(=Y')R^{16}$, -$(CR^{19}R^{20})_n$ $C(=Y')OR^{16}$, -$(CR^{19}R^{20})_nC(=Y')NR^{16}R^{17}$, -$(CR^{19}R^{20})_nNR^{16}R^{17}$, -$(CR^{19}R^{20})_nOR^{16}$, -$(CR^{19}R^{20})_nSR^{16}$, -$(CR^{19}R^{20})_nNR^{16}C(=Y')R^{17}$, -$(CR^{19}R^{20})_nNR^{16}C(=Y')OR^{17}$, -$(CR^{19}R^{20})_nNR^{18}C(=Y4)NR^{16}R^{17}$, -$(CR^{19}R^{20})_nNR^{17}SO_2R^{16}$, -$(CR^{19}R^{20})_nOC(=Y')R^{16}$, -$(CR^{19}R^{20})_nOC(=Y')OR^{16}$, -$(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, -$(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, -$(CR^{19}R_{20})_nOP(=Y')(OR^{16})(OR^{17})$, -$(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, -$(CR^{19}R^{20})_nS(O)R^{16}$ -$(CR^{19}R^{20})_nS(O)_2R^{16}$, -$(CR^{19}R^{20})_nS(O)_2NR^{16}R^{17}$, -$(CR^{19}R^{20})_nS(O)(OR^{16})$, -$(CR^{19}R^{20})_n$ $S(O)_2(OR^{16})$, -$(CR^{19}R^{20})SC(=Y')R^{16}$, -$(CR^{19}R^{20})_nSC(=Y')OR^{16}$, -$(CR^{19}R^{20})_n$ $SC(=Y')NR^{16}R^{17}$ und R^{21} ausgewählten Gruppen substituiert ist;

R^{16}, R^{17} und R^{18} jeweils unabhängig H, C_{1-12}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Carbocyclyl, Heterocyclyl, Aryl oder Heteroaryl sind, worin das Alkyl, Alkenyl, Alkinyl, Carbocyclyl, Heterocyclyl, Aryl oder Heteroaryl gegebenenfalls mit einer oder mehreren aus Halogen, CN, -OCF_3, CF_3, -NO_2, C_{1-6}-Alkyl, -OH, -SH, -O(C_{1-6}-Alkyl), -S(C_{1-6}-Alkyl), -NH_2, -NH(C_{1-6}-Alkyl), -N(C_{1-6}-Alkyl)$_2$, SO_2(C_{1-6}-Alkyl), -CO_2H, -CO_2(C_{1-6}-Alkyl), -C(O)NH_2, -C(O)NH(C_{1-6}-Alkyl), -C(O)N(C_{1-6}-Alkyl)$_2$, -N(C_{1-6}-Alkyl)C(O)(C_{1-6}-alkyl), -NHC(O)(C_{1-6}-Alkyl), $NHSO_2$(C_{1-6}-Alkyl), -N(C_{1-6}-Alkyl)SO_2(C_{1-6}-alkyl), -SO_2NH_2, -SO_2NH(C_{1-6}-Alkyl), -SO_2N(C_{1-6}-Alkyl)$_2$, -OC(O)NH_2, -OC(O)NH(C_{1-6}-Alkyl), -OC(O)-N(C_{1-6}-Alkyl)$_2$, -N(C_{1-6}-Alkyl)C(O)NH(C_{1-6}-alkyl), -N(C_{1-6}-Alkyl)C(O)N(C_{1-6}-alkyl)$_2$, -NHC(O)NH(C_{1-6}-Alkyl), -NHC(O)N(C_{1-6}-Alkyl)$_2$, -NHC(O)O(C_{1-6}-Alkyl) und -N(C_{1-6}-Alkyl)C(O)O(C_{1-6}-Alkyl) ausgewählten Gruppen substituiert ist;

oder R^{16} und R^{17} zusammen mit Stickstoffatom, an das sie gebunden sind, einen 3- bis 8-gliedrigen, gesättigten oder ungesättigten Ring mit 0 bis 2 zusätzlichen, aus O, S und N ausgewählten Heteroatomen bilden, worin der Ring gegebenenfalls mit einer oder mehreren, aus Halogen, CN, -OCF_3, CF_3, -NO_2, C_{1-6}-Alkyl, -OH, -SH, -O(C_{1-6}-Alkyl), -S(C_{1-6}-Alkyl), -NH_2, -NH(C_{1-6}-Alkyl), -N(C_{1-6}-Alkyl)$_2$, SO_2(C_{1-6}-Alkyl), -CO_2H, -CO_2(C_{1-6}-Alkyl), -C(O)NH_2, -C(O)NH(C_{1-6}-Alkyl), -C(O)-N(C_{1-6}-Alkyl)$_2$, -N(C_{1-6}-Alkyl)C(O)(C_{1-6}-alkyl), -NHC(O)(C_{1-6}-Alkyl), $NHSO_2$(C_{1-6}-Alkyl), -N(C_{1-6}-Alkyl)SO_2(C_{1-6}-alkyl), -SO_2NH_2, -SO_2NH(C_{1-6}-Alkyl), -SO_2N(C_{1-6}-Alkyl)$_2$, -OC(O)NH_2, -OC(O)NH(C_{1-6}-Alkyl), -OC(O)N(C_{1-6}-Alkyl)$_2$, -N(C_{1-6}-Alkyl)C(O)NH(C_{1-6}-alkyl), -N(C_{1-6}-Alkyl)C(O)N(C_{1-6}-alkyl)$_2$, -NHC(O)NH(C_{1-6}-Alkyl), -NHC(O)N(C_{1-6}-Alkyl)$_2$,- NHC(O)O(C_{1-6}-Alkyl) und -N(C_{1-6}-Alkyl)C(O)O(C_{1-6}-Alkyl) ausgewählten Gruppen substituiert ist;

R^{19} und R^{20} jeweils unabhängig aus H, C_{1-12}-Alkyl, -$(CH_2)_n$-Aryl, -$(CH_2)_n$-Carbocyclyl, -$(CH_2)_n$-Heterocyclyl und -$(CH_2)_n$-Heteroaryl ausgewählt sind;

R^{21} C_{1-12}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Carbocyclyl, Heterocyclyl, Aryl oder Heteroaryl sind, wobei jeder Vertreter von R^{21} gegebenenfalls mit einer oder mehreren, aus Halogen, Oxo, CN, -OCF_3, CF_3, -NO_2, C_{1-6}-Alkyl, -OH, -SH, -O(C_{1-6}-Alkyl), -S(C_{1-6}-Alkyl), -NH_2, -NH(C_{1-6}-Alkyl), -N(C_{1-6}-Alkyl)$_2$, SO_2(C_{1-6}-Alkyl), -CO_2H, -CO_2(C_{1-6}-Alkyl), -C(O)NH_2, -C(O)NH(C_{1-6}-Alkyl), -C(O)N(C_{1-6}-Alkyl)$_2$, -N(C_{1-6}-Alkyl)-C(O)(C_{1-6}-alkyl), -NHC(O)(C_{1-6}-Alkyl), $NHSO_2$(C_{1-6}-Alkyl), -N(C_{1-6}-Alkyl)SO_2(C_{1-6}-alkyl), -SO_2NH_2, -SO_2NH(C_{1-6}-Alkyl), -SO_2N(C_{1-6}-Alkyl)$_2$, -OC(O)NH_2, -OC(O)NH(C_{1-6}-Alkyl), -OC(O)N(C_{1-6}-Alkyl)$_2$, -N(C_{1-6}-Alkyl)C(O)NH(C_{1-6}-alkyl), -N(C_{1-6}-Alkyl)C(O)-N(C_{1-6}-alkyl)$_2$, -NHC(O)NH(C_{1-6}-Alkyl), -NHC(O)N(C_{1-6}-Alkyl)$_2$, -NHC(O)O(C_{1-6}-Alkyl) und -N(C_{1-6}-Alkyl)C(O)O(C_{1-6}-Alkyl) ausgewählten Gruppen substituiert ist;

die Y' jeweils unabhängig O, NR^{22} oder S sind; und

R^{22} = H oder C_{1-12}-Alkyl ist.

Revendications

1. Composé pour une utilisation dans un procédé pour le traitement d'un cancer, qui est choisi entre :

   le (2-hydroxyéthoxy)-amide d'acide 5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
   le ((R)-2,3-dihydroxy-propoxy)-amide d'acide 5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
   le ((S)-2-hydroxy-propoxy)-amide d'acide 5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
   le (2-hydroxyéthoxy)-amide d'acide 5-(4-bromo-2-fluoro-phénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
   le ((S)-2-hydroxy-propoxy)-amide d'acide 5-(4-bromo-2-fluorophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
   le ((S)-2-hydroxy-propoxy)-amide d'acide 5-(4-bromo-2-fluorophénylamino)-8-fluoro-imidazo[1,5-a]pyridine-6-carboxylique ;
   le (2-hydroxy-éthoxy)-amide d'acide 8-fluoro-5-(2-fluoro-4-iodo-phénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
   le ((R)-2,3-dihydroxy-propoxy)-amide d'acide 8-fluoro-5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
   le ((S)-2-hydroxy-propoxy)-amide d'acide 8-fluoro-5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
   le (2-hydroxy-éthoxy)-amide d'acide 5-(2-fluoro-méthane-sulfanyl-phénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
   le (2-hydroxy-éthoxy)-amide d'acide 5-(2-fluoro-4-iodo-phénylamino)-imidazo[1,5-a]pyrazine-6-carboxylique ;
   le ((S)-2-hydroxy-propoxy)-amide d'acide 5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyrazine-6-carboxylique ;
   le (2-hydroxy-éthoxy)-amide d'acide 5-(4-cyclopropyl-2-fluorophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
   le (R)-N-(2,3-dihydroxypropoxy)-5-(2-fluoro-4-iodophényl-amino)imidazo[1,5-a]pyrazine-6-carboxamide ;
   le N-éthoxy-5-(2-fluoro-4-iodophénylamino)imidazo[1,5-a]-pyrazine-6-carboxamide ;
   le N-(cyclopropylméthoxy)-5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyrazine-6-carboxamide ;
   le 5-(2-fluoro-4-iodophénylamino)-N-méthylimidazo[1,5-a]-pyrazine-6-carboxamide ;
   le 5-(4-bromo-2-fluorophénylamino)-N-(2-hydroxy-éthoxy)-imidazo[1,5-a]pyrazine-6-carboxamide ;
   le (S)-5-(4-bromo-2-fluorophénylamino)-N-(2-hydroxy-propoxy)imidazo[1,5-a]pyrazine-6-carboxamide ;
   le (R)-5-(4-bromo-2-fluorophénylamino)-N-(2,3-dihydroxy-propoxy)imidazo[1,5-a]pyrazine-6-carboxamide ; et
   le 5-(4-bromo-2-fluorophénylamino)-N-(cyclopropyl-méthoxy)imidazo[1,5-a]pyrazine-5-carboxamide ; ou un de ses sels pharmaceutiquement acceptables ;
   le procédé comprenant l'administration du composé en association avec la gemcitabine ou un taxoïde.

2. Composé pour une utilisation dans un procédé pour le traitement d'un cancer suivant la revendication 1, le composé étant le (2-hydroxyéthoxy)-amide d'acide 5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ou un de ses sels pharmaceutiquement acceptables.

3. Composé pour une utilisation dans un procédé pour le traitement d'un cancer suivant la revendication 1 ou la revendication 2, le cancer étant le cancer du pancréas, le cancer pulmonaire non à petites cellules, le cancer colorectal, le cancer de l'endomètre, le cancer des ovaires ou un mélanome malin.

4. Composé pour une utilisation dans un procédé pour le traitement d'un cancer suivant l'une quelconque des revendications 1 à 3, le composé étant administré simultanément avec le taxoïde ou la gemcitabine.

5. Composé pour une utilisation dans un procédé pour le traitement d'un cancer suivant l'une quelconque des revendications 1 à 3, le composé étant administré séquentiellement par rapport au taxoïde ou à la gemcitabine.

6. Composé pour une utilisation dans un procédé pour le traitement d'un cancer suivant l'une quelconque des revendications 1 à 3, le composé étant administré séparément du taxoïde ou de la gemcitabine.

7. Composé pour une utilisation dans un procédé pour le traitement d'un cancer suivant l'une quelconque des revendications précédentes, le taxoïde étant le paclitaxel.

8. Composé pour une utilisation dans un procédé pour le traitement d'un cancer suivant l'une quelconque des revendications précédentes, le traitement étant destiné à l'administration orale.

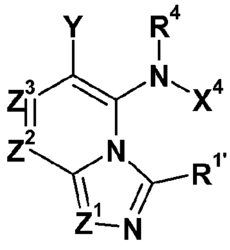
9. Composé pour une utilisation dans un procédé pour le traitement d'un cancer suivant l'une quelconque des revendications 1 à 3, le composé étant destiné à l'administration en association avec la gemcitabine pour le traitement du cancer du pancréas.

10. Composé pour une utilisation dans un procédé pour le traitement d'un cancer suivant l'une quelconque des revendications 1 à 3, le composé étant destiné à l'administration en association avec le paclitaxel pour le traitement du cancer pulmonaire non à petites cellules ou le cancer des ovaires.

11. Composé pour une utilisation dans un procédé pour le traitement d'un cancer ou d'un trouble inflammatoire **caractérisé par** une mutation ou surexpression de la kinase MEK, le composé étant choisi entre :

le (2-hydroxyéthoxy)-amide d'acide 5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
le ((R)-2,3-dihydroxy-propoxy)-amide d'acide 5-(2-fluoro-4-iodophénylamino)-imidazo [1, 5-a]pyridine-6-carboxyliq ue ;
le ((S)-2-hydroxy-propoxy)-amide d'acide 5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
le (2-hydroxyéthoxy)-amide d'acide 5-(4-bromo-2-fluoro-phénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
le ((S)-2-hydroxy-propoxy)-amide d'acide 5-(4-bromo-2-fluorophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
le ((S)-2-hydroxy-propoxy)-amide d'acide 5-(4-bromo-2-fluorophénylamino)-8-fluoro-imidazo[1,5-a]pyridine-6-carboxylique ;
le (2-hydroxy-éthoxy)-amide d'acide 8-fluoro-5-(2-fluoro-4-iodo-phénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
le ((R)-2,3-dihydroxy-propoxy)-amide d'acide 8-fluoro-5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
le ((S)-2-hydroxy-propoxy)-amide d'acide 8-fluoro-5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
le (2-hydroxy-éthoxy)-amide d'acide 5-(2-fluoro-méthane-sulfanyl-phénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
le (2-hydroxy-éthoxy)-amide d'acide 5-(2-fluoro-4-iodo-phénylamino)-imidazo[1,5-a]pyrazine-6-carboxylique ;
le ((S)-2-hydroxy-propoxy)-amide d'acide 5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyrazine-6-carboxylique ;
le (2-hydroxy-éthoxy)-amide d'acide 5-(4-cyclopropyl-2-fluorophénylamino)-imidazo[1,5-a]pyridine-6-carboxylique ;
le (R)-N-(2,3-dihydroxypropoxy)-5-(2-fluoro-4-iodophényl-amino)imidazo[1,5-a]pyrazine-6-carboxamide ;
le N-éthoxy-5-(2-fluoro-4-iodophénylamino)imidazo[1,5-a]-pyrazine-6-carboxamide ;
le N-(cyclopropylméthoxy)-5-(2-fluoro-4-iodophénylamino)-imidazo[1,5-a]pyrazine-6-carboxamide ;
le 5-(2-fluoro-4-iodophénylamino)-N-méthylimidazo[1,5-a]-pyrazine-6-carboxamide ;
le 5-(4-bromo-2-fluorophénylamino)-N-(2-hydroxy-éthoxy)-imidazo[1,5-a]pyrazine-6-carboxamide ;
le (S)-5-(4-bromo-2-fluorophénylamino)-N-(2-hydroxy-propoxy)imidazo[1,5-a]pyrazine-6-carboxamide ;
le (R)-5-(4-bromo-2-fluorophénylamino)-N-(2,3-dihydroxy-propoxy)imidazo[1,5-a]pyrazine-6-carboxamide ; et
le 5-(4-bromo-2-fluorophénylamino)-N-(cyclopropyl-méthoxy)imidazo[1,5-a]pyrazine-6-carboxamide ; ou un de ses sels pharmaceutiquement acceptables.

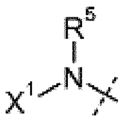
12. Composé représenté par la formule I, et ses sels, pour une utilisation dans un procédé pour le traitement d'un trouble inflammatoire :



I

formule dans laquelle :

Z^1 représente un groupe CR^1 ou N ;
R^1 représente H, un groupe alkyle en C_1 à C_3, halogéno, CF_3, CHF_2, CN, OR^A ou NR^AR^A ;
$R^{1'}$ représente H, un groupe alkyle en C_1 à C_3, halogéno, CF_3, CHF_2, CN, OR^A ou NR^AR^A ;
chaque groupe R^A représentant indépendamment H ou un groupe alkyle en C_1 à C_3 ;
Z^2 représente un groupe CR^2 ou N ;
Z^3 représente un groupe CR^3 ou N ; sous réserve qu'un seul de Z^1, Z^2 et Z^3 puisse représenter N en même temps ;
R^2 et R^3 sont choisis indépendamment entre H, des groupes halogéno, CN, CF_3, $-OCF_3$, $-NO_2$, $-(CR^{14}R^{15})_nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{11}R^{12}$, $-(CR^{14}R^{15})_nOR^{11}$, $-(CR^{14}R^{15})_nSR^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')R^{11}$, $-(CR^{14}R^{15})_n-NR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_nNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nNR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nOC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_nOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_nOP(=Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nOP-(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_n-S(O)_2NR^{11}R^{12}$, $-(CR^{14}R^{15})_nS(O)(OR^{11})$, $-(CR^{14}R^{15})_nS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_n-SC(=Y')R^{11}$, $-(CR^{14}R^{15})_nSC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nSC(=Y')NR^{11}R^{12}$, alkyle en C_1 à C_{12}, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, carbocyclyle, hétérocyclyle, aryle, et hétéroaryle ;
R^4 représente H, un groupe alkyle en C_1 à C_6 ou carbocyclyle en C_3 ou $_4$;
Y représente un groupe W-C(O)- ou W' ;
W représente un groupe



ou

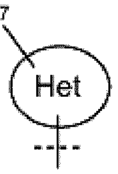
R^5 représente H ou un groupe alkyle en C_1 à C_{12} ;
X^1 est choisi entre des groupes $R^{11'}$ et $-OR^{11'}$; lorsque X^1 représente un groupe $R^{11'}$, X^1 est facultativement pris conjointement avec R^5 et l'atome d'azote auquel ils sont liés pour former un noyau tétra- à heptagonal saturé ou insaturé comprenant 0 à 2 hétéroatomes supplémentaires choisis entre 0, S et N, ledit noyau étant facultativement substitué avec un ou plusieurs groupes choisis entre des groupes halogéno, CN, CF_3, $-OCF_3$, $-NO_2$, OXO, $-(CR^{19}R^{20})_n-C(=Y')R^{16}$, $-(CR^{19}R^{20})_nC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_n-NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_nSR^{16}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_nNR^{18}C(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_n-NR^{17}SO_2R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')OR^{16}$, $-(CR^{19}R^{20})n-OC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nS(O)R^{16}$, $-(CR^{19}R^{20})_nS(O)_2R^{16}$, $-(CR^{19}R^{20})_n(O)_2NR^{16}R^{17}$, $-(CR^{19}R^{20})_nS\ (O)(OR^{16})$, $-(CR^{19}R^{20})_nS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nSC(=Y')R^{16}$, $-(CR^{19}R^{20})_nSC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nSC(=Y')-NR^{16}R^{17}$, et R^{21};
chaque groupe $R^{11'}$ représente indépendamment H, un groupe alkyle en C_1 à C_{12}, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, carbocyclyle, hétérocyclyle, aryle ou hétéroaryle ;

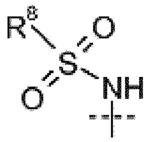
R^{11}, R^{12} et R^{13} représentent indépendamment H, un groupe alkyle en C_1 à C_{12}, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, carbocyclyle, hétérocyclyle, aryle ou hétéroaryle ;

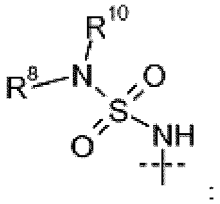
ou bien R^{11} et R^{12}, conjointement avec l'atome d'azote auquel ils sont fixés, forment un noyau tri- à octogonal saturé, insaturé ou aromatique comprenant 0 à 2 hétéroatomes choisis entre 0, S et N, ledit noyau étant facultativement substitué avec un ou plusieurs groupes choisis entre des groupes halogéno, CN, CF_3, $-OCF_3$, $-NO_2$, alkyle en C_1 à C_6, -OH, - SH, -0 (alkyle en C_1 à C_6), -S (alkyle en C_1 à C_6), $-NH_2$, - NH (alkyle en C_1 à C_6), -N (alkyle en C_1 à $C_6)_2$, $-SO_2$ (alkyle en C_1 à C_6) , $-CO_2H$, $-CO_2$ (alkyle en Ci à C_6) , $-C(O)NH_2$, -C(O)-NH(alkyle en C_1 à C_6), -C(O)N(alkyle en C_1 à $C_6)_2$, -N (alkyle en C_1 à C_6)C(O) (alkyle en C_1 à C_6), -NHC(O) (alkyle en C_1 à C_6), $-NHSO_2$ (alkyle en C_1 à C_6), -N (alkyle en C_1 à C_6)SO_2 (alkyle en C_1 à C_6), $-SO_2NH_2$, $-SO_2NH$ (alkyle en C_1 à C_6), $-SO_2N$ (alkyle en C_1 à $C_6)_2$, $-OC(O)NH_2$, -OC(O)NH(alkyle en C_1 à C_6), -OC(O)N-(alkyle en C_1 à $C_6)_2$, -OC(O)O(alkyle en C_1 à C_6), -NHC(O)NH-(alkyle en C_1 à C_6), -NHC(O)N(alkyle en C_1 à $C_6)_2$, -N(alkyle en C_1 à C_6)C(O)NH(alkyle en C_1 à C_6), -N(alkyle en C_1 à C_6)-C(O)N(alkyle en C_1 à $C_6)_2$, -NHC(O)NH(alkyle en C_1 à C_6), -NHC(O)N(alkyle en C_1 à $C_6)_2$, -NHC(O)O(alkyle en C_1 à C_6) et -N(alkyle en C_1 à C_6)C(O)O(alkyle en C_1 à C_6);

R^{14} et R^{15} sont choisis indépendamment entre H, des groupes alkyle en C_1 à C_{12}, aryle, carbocyclyle, hétérocyclyle et hétéroaryle ;

W' représente un groupe



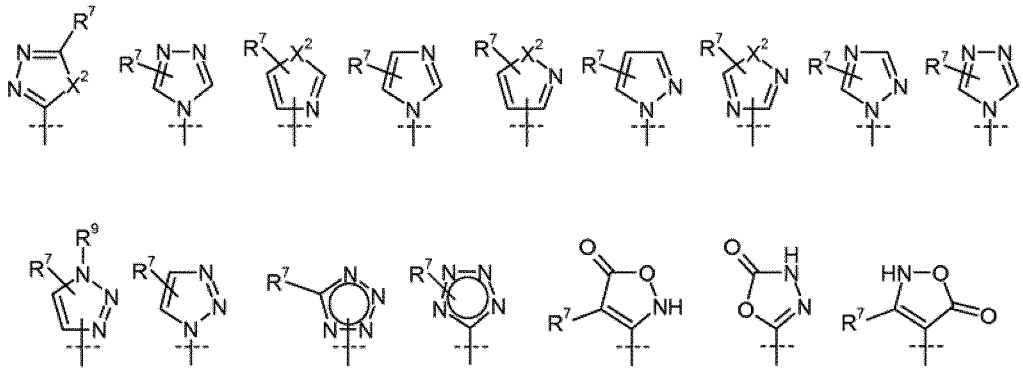




;

dans lequel

représente un groupe



chaque groupe X^2 représente indépendamment 0, S ou un groupe NR^9 ;

chaque groupe R^7 est choisi indépendamment entre H, des groupes halogéno, CN, CF_3, $-OCF_3$, $-NO_2$, -

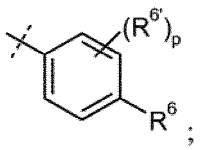
$(CR^{14}R^{15})_n-C(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_n-NR^{11}R^{12}$, $(CR^{14}R^{15})_nOR^{11}$, $-(CR^{14}R^{15})_nSR^{11}$, $-(CR^{14}R^{15})_nNR^{12}C(=Y')R^{11}$, - $(CR^{14}R^{15})_nNR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_nNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_n-NR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')R^{11}$, $-(CR^{14}R^{15})_nOC(=Y')OR^{11}$, $-(CR^{14}R^{15})_n-OC(=Y')NR^{11}R^{12}$,- $(CR^{14}R^{15})_nOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_nOP(=Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_nS(O)_2NR^{11}R^{12}$, $-(CR^{14}R^{15})_nS(O)(OR^{11})$, $-(CR^{14}R^{15})_nS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_nSC(=Y')R^{11}$, $-(CR^{14}R^{15})_nSC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nSC(=Y^1)-NR^{11}R^{12}$, alkyle en C_1 à C_{12}, alcényle en C_2 à C_8 alcynyle en C_2 à C_8, carbocyclyle, hétérocyclyle, aryle, et hétéroaryle ;

chaque groupe R^8 est choisi indépendamment entre des groupes alkyle en C_1 à C_{12}, aryle, carbocyclyle, hétérocyclyle et hétéroaryle ;

R^9 est choisi entre H, des groupes $-(CR^{14}R^{15})_nC(=Y')R^{11}$, $-(CR^{14}R^{15})_nC(=Y')OR^{11}$, $-(CR^{14}R^{15})_nC(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_qNR^{11}R^{12}$, $-(CR^{14}R^{15})_qOR^{11}$, $-(CR^{14}R^{15})_qSR^{11}$, $-(CR^{14}R^{15})_qNR^{12}C(=Y')R^{11}$, $-(CR^{14}R^{15})_q-NR^{12}C(=Y')OR^{11}$, $-(CR^{14}R^{15})_qNR^{13}C(=Y')NR^{11}R^{12}$, $-(CR^{14}R^{15})_qNR^{12}SO_2R^{11}$, $-(CR^{14}R^{15})_qOC(=Y')R^{11}$, $-(CR^{14}R^{15})_qOC(=Y')OR^{11}$, $-(CR^{14}R^{15})_qOC(=Y')-NR^{11}R^{12}$, $-(CR^{14}R^{15})_qOS(O)_2(OR^{11})$, $-(CR^{14}R^{15})_qOP(=Y')(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_qOP(OR^{11})(OR^{12})$, $-(CR^{14}R^{15})_nS(O)R^{11}$, $-(CR^{14}R^{15})_nS(O)_2R^{11}$, $-(CR^{14}R^{15})_nS(O)_2NR^{11}R^{12}$, alkyle en C_1 à C_{12}, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, carbocyclyle, hétérocyclyle, aryle et hétéroaryle ;

R^{10} représente H, un groupe alkyle en C_1 à C_6 ou carbocyclyle en C_3 ou C_4 ;

X^4 représente un groupe



;

R^6 représente H, un groupe halogéno, alkyle en C_1 à C_6, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, carbocyclyle, hétéroaryle, hétérocyclyle, $-OCF_3$, $-NO_2$, -Si(alkyle en C_1 à C_6), $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, ou $-(CR^{19}R^{20})_n-SR^{16}$;

$R^{6'}$ représente H, un groupe halogéno, alkyle en C_1 à C_6, carbocyclyle, CF_3, $-OCF_3$, $-NO_2$, -Si (alkyle en C_1 à C_6), $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_n-SR^{16}$, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, hétérocyclyle, aryle ou hétéroaryle ;

p est égal à 0, 1, 2 ou 3 ;

n est égal à 0, 1, 2 ou 3 ;

q est égal à 2 ou 3 ;

où chacun desdits groupes alkyle, alcényle, alcynyle, carbocyclyle, hétérocyclyle, aryle et hétéroaryle de R^1, R^2, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, R^8, R^9, R^{10}, R^{11}, $R^{11'}$, R^{12}, R^{13}, R^{14}, R^{15} et R^A est facultativement substitué indépendamment avec un ou plusieurs groupes choisis indépendamment entre des groupes halogéno, CN, CF_3, $-OCF_3$, $-NO_2$, oxo, -Si(alkyle en C_1 à C_6), $-(CR^{19}R^{20})_nC(=Y')R^{16}$, $-(CR^{19}R^{20})_nC(=Y')OR^{16}$, $-(CR^{19}R^{20})_n-C(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{16}R^{17}$, $-(CR^{19}R^{20})_nOR^{16}$, $-(CR^{19}R^{20})_nSR^{16}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')R^{17}$, $-(CR^{19}R^{20})_nNR^{16}C(=Y')OR^{17}$, $-(CR^{19}R^{20})_nNR^{18}C-(=Y')$ $NR^{16}R^{17}$, $-(CR^{19}R^{20})_nNR^{17}SO_2R^{16}$, $-(CR^{19}R^{20})_nOC(=Y')R^{16}$, $-(CR^{19}R^{20})_n-OC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nOC(=Y')NR^{16}R^{17}$, $-(CR^{19}R^{20})_nOS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nOP(=Y')(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_nOP(OR^{16})(OR^{17})$, $-(CR^{19}R^{20})_n-S(O)R^{16}$, $-(CR^{19}R^{20})_nS(O)_2R^{16}$, $-(CR^{19}R^{20})_nS(O)_2NR^{16}R^{17}$, $-(CR^{19}R^{20})_n-S(O)(OR^{16})$, $-(CR^{19}R^{20})_nS(O)_2(OR^{16})$, $-(CR^{19}R^{20})_nSC(=Y')R^{16}$, $-(CR^{19}R^{20})_n-SC(=Y')OR^{16}$, $-(CR^{19}R^{20})_nSC(=Y')NR^{16}R^{17}$ et R^{21} ;

chacun de R^{16}, R^{17} et R^{18} représente indépendamment H, un groupe alkyle en C_1 à C_{12}, alcényle en C_2 à C_8, alcynyle en C_2 à C_3, carbocyclyle, hétérocyclyle, aryle ou hétéroaryle, lesdits groupes alkyle, alcényle, alcynyle, carbocyclyle, hétérocyclyle, aryle et hétéroaryle étant facultativement substitués avec un ou plusieurs groupes choisis entre des groupes halogéno, CN, $-OCF_3$, CF_3, $-NO_2$, alkyle en C1 à C6, -OH, -SH, -O(alkyle en C_1 à C_6), -S(alkyle en C_1 à C_6), $-NH_2$, -NH (alkyle en C_1 à C_6), -N (alkyle en C_1 à C_6)$_2$, $-SO_2$(alkyle en C_1 à C_6, $-CO_2H$, $-CO_2$(alkyle en C_1à C_6), $-C(O)NH_2$, -C(O)NH(alkyle en C_1 à C_6), -C(O)N(alkyle en C_1 à C_6)$_2$, -N (alkyle en C_1 à C_6)C(O) (alkyle en C_1 à C_6), -NHC(O) (alkyle en C_1 à C_6), $NHSO_2$ (alkyle en C_1 à C_6), -N (alkyle en C_1 à C_6)SO_2 (alkyle en C_1 à C_6), $-SO_2NH_2$, $-SO_2NH$ (alkyle en C_1 à C_6), $-SO_2N$(alkyle en C_1 à C_6)$_2$, $-OC(O)NH_2$, -OC(O)NH(alkyle en C_1 à C_6), -OC(O)N(alkyle en C_1 à C_6)$_2$, -OC(O)O(alkyle en C_1 à C_6), -NHC(O)NH (alkyle en C_1 à C_6), -NHC(O)N (alkyle en C_1 à C_6)$_2$, -N (alkyle en C_1 à C_6)C(O)NH (alkyle en C_1 à C_6), -N (alkyle en C_1 à C_6) C(O)N (alkyle en C_1 à C_6)$_2$, -NHC(O)NH (alkyle en C_1 à C_6), -NHC(O)N(alkyle en C_1 à C_6)$_2$, -NHC(O)O(alkyle en C_1 à C_6) et -N (alkyle en C_1 à C_6)C(O)O(alkyle en C_1 à C_6) ;

ou bien R^{16} et R^{17}, conjointement avec l'atome d'azote auquel ils sont fixés, forment un noyau tri- à octogonal saturé, insaturé ou aromatique comprenant 0 à 2 hétéroatomes choisis entre 0, S et N, ledit noyau étant facultativement substitué avec un ou plusieurs groupes choisis entre des groupes halogéno, CN, $-OCF_3$, CF_3, $-NO_2$, alkyle en C_1 à C_6, -OH, -SH, -0 (alkyle en C_1 à C_6), -S (alkyle en C_1 à C_6), $-NH_2$, -NH (alkyle en C_1 à C_6), -N (alkyle en C_1 à $C_6)_2$, $-SO_2$ (alkyle en C_1 à C_6), $-CO_2H$, $-CO_2$ (alkyle en C_1 à C_6), $-C(O)NH_2$, -C(O)NH(alkyle en C_1 à C_6), -C(O)N(alkyle en C_1 à $C_6)_2$, -N (alkyle en C_1 à C_6)C(O) (alkyle en C_1 à C_6), -NHC(O)(alkyle en C_1 à C_6), $-NHSO_2$ (alkyle en C_1 à C_6), -N (alkyle en C_1 à $C_6)SO_2$(alkyle en C_1 à C_6), $-SO_2NH_2$, $-SO_2NH$ (alkyle en C_1 à C_6), $-SO_2N$(alkyle en C_1 à $C_6)_2$, $-OC(O)NH_2$, -OC(O)NH(alkyle en C_1 à C_6), -OC(O)N(alkyle en C_1 à $C_6)_2$, -OC(O)O(alkyle en C_1 à C_6), -NHC(O)NH (alkyle en C_1 à C_6), -NHC(O)N (alkyle en C_1 à $C_6)_2$, -N (alkyle en C_1 à C_6)C(O)NH (alkyle en C_1 à C_6), -N (alkyle en C_1 à C_6)C(O)N (alkyle en C_1 à $C_6)_2$, -NHC(O)NH-(alkyle en C_1 à C_6), -NHC(O)N (alkyle en C_1 à $C_6)_2$, -NHC(O)O-(alkyle en C_1 à C_6) et -N(alkyle en C_1 à C_6)C(O)O(alkyle en C_1 à C_6) ;

R^{19} et R^{20} sont choisis indépendamment entre H, des groupes alkyle en C_1 à C_{12}, - $(CH_2)_n$-aryle, $-(CH_2)_n$-carbocyclyle, - $(CH_2)_n$-hétérocyclyle et $-(CH_2)_n$-hétéroaryle ;

R^{21} représente un groupe alkyle en C_1 à C_{12}, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, carbocyclyle, hétérocyclyle, aryle ou hétéroaryle, où chaque membre de R^{21} est facultativement substitué avec un ou plusieurs groupes choisis entre des groupes halogéno, oxo, CN, $-OCF_3$, CF_3, $-NO_2$, alkyle en C_1 à C_6, -OH, -SH, -0 (alkyle en C_1 à C_6), -S(alkyle en C_1 à C_6), $-NH_2$, -NH (alkyle en C_1 à C_6), -N (alkyle en C_1 à $C_6)_2$, $-SO_2$ (alkyle en C_1 à C_6), $-CO_2H$, $-CO_2$ (alkyle en C_1 à C_6), $-C(O)NH_2$, -C(O)NH (alkyle en C_1 à C_6), -C(O)N (alkyle en C_1 à $C_6)_2$, -N (alkyle en C_1 à C_6)C(O)-(alkyle en C_1 à C_6), -NHC(O) (alkyle en C_1 à C_6), $-NHSO_2$-(alkyle en C_1 à C_6), -N (alkyle en C_1 à $C_6)SO_2$ (alkyle en C_1 à C_6),- SO_2NH_2, $-SO_2NH$ (alkyle en C_1 à C_6), $-SO_2N$ (alkyle en C_1 à $C_6)_2$, $-OC(O)NH_2$, -OC(O)NH(alkyle en C_1 à C_6), -OC(O)N(alkyle en C_1 à $C_6)_2$, -OC(O)O(alkyle en C_1 à C_6), -NHC(O)NH(alkyle en C_1 à C_6), -NHC(O)N(alkyle en C_1 à $C_6)_2$, -N (alkyle en C_1 à C_6)C(O)NH-(alkyle en C_1 à C_6), -N(alkyle en C_1 à C_6)C(O)N(alkyle en C_1 à $C_6)_2$, -NHC(O)NH(alkyle en C_1 à C_6), -NHC(O)N(alkyle en C_1 à $C_6)_2$, -NHC(O)O(alkyle en C_1 à C_6) et -N (alkyle en C_1 à C_6)C(O)O(alkyle en C_1 à C_6) ;

chaque groupe Y' représente indépendamment 0, un groupe NR^{22} ou S ; et

R^{22} représente H ou un groupe alkyle en C_1 à C_{12}.

REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

- WO 0105390 A **[0004]**
- WO 0206213 A **[0005]**
- WO 03077855 A **[0005]**
- WO 03077914 A **[0005]**
- US 2005153942 A **[0005]**
- US 2005049276 A **[0005]**
- WO 9633172 A **[0026]**
- WO 9627583 A **[0026]**
- EP 818442 A **[0026]**
- EP 1004578 A **[0026]**
- WO 9807697 A **[0026]**
- WO 9803516 A **[0026]**
- WO 9834918 A **[0026]**
- WO 9834915 A **[0026]**
- WO 9833768 A **[0026]**
- WO 9830566 A **[0026]**
- EP 606046 A **[0026]**
- EP 931788 A **[0026]**
- WO 9005719 A **[0026]**
- WO 9952910 A **[0026]**
- WO 9952889 A **[0026]**
- WO 9929667 A **[0026]**
- WO 9907675 A **[0026]**
- EP 945864 A **[0026]**
- US 5863949 A **[0026]**
- US 5861510 A **[0026]**
- EP 780386 A **[0026]**
- WO 0132651 A **[0026]**
- WO 0047212 A **[0026]**
- WO 9835985 A **[0026]**
- WO 0160814 A **[0026]**
- WO 9722596 A **[0026]**
- WO 9730035 A **[0026]**
- WO 9732856 A **[0026]**
- WO 9813354 A **[0026]**
- US 7173029 B **[0027]**
- US 7037915 B **[0027]**
- US 6608056 B **[0027]**
- US 6608053 B **[0027]**
- US 6838457 B **[0027]**
- US 6770641 B **[0027]**
- US 6653320 B **[0027]**
- US 6403588 B **[0027]**
- US 20080242665 A **[0027]**
- WO 2006046031 A **[0027]**
- WO 2006046035 A **[0027]**
- WO 2006046040 A **[0027]**
- WO 2007042806 A **[0027]**
- WO 2007042810 A **[0027]**
- WO 2004017950 A **[0027]**
- US 2004092561 A **[0027]**
- WO 2004007491 A **[0027]**
- WO 2004006916 A **[0027]**
- WO 2003037886 A **[0027]**
- US 2003149074 A **[0027]**
- WO 2003035618 A **[0027]**
- WO 2003034997 A **[0027]**
- US 2003158212 A **[0027]**
- EP 1417976 A **[0027]**
- US 2004053946 A **[0027]**
- JP 2001247477 B **[0027]**
- JP 08175990 B **[0027]**
- JP 08176070 B **[0027]**
- US 6703414 B **[0027]**
- WO 9715658 A **[0027]**

Non-patent literature cited in the description

- **AHN et al.** *Methods in Enzymology,* 2001, vol. 332, 417-431 **[0002]**
- **KHOKHLATCHEV et al.** *Cell,* 1998, vol. 93, 605-615 **[0002]**
- **AHN et al.** *Molecular Cell,* 2000, vol. 6, 1343-1354 **[0002]**
- **LEWIS et al.** *Adv. Cancer Res.,* 1998, vol. 74, 49-139 **[0002]**
- **KOHL et al.** *Science,* 1993, vol. 260, 1834-1837 **[0003]**
- **DAVIES, H. et al.** *Nature,* 2002, vol. 417, 949-954 **[0003]**
- **HOSHINO, R. et al.** *Oncogene,* 1999, vol. 18, 813-822 **[0003]**
- **SEBOLT-LEOPOLD et al.** *Nature-Medicine,* 1999, vol. 5 (7), 810-816 **[0004]**
- **TRACHET et al.** *AACR,* 06 April 2002 **[0004]**
- **TECLE, H.** *IBC 2.sup.nd International Conference of Protein Kinases,* 09 September 2002 **[0004]**
- **MILELLA et al.** *J Clin Invest,* 2001, vol. 108 (6), 851-859 **[0004]**
- **PAQUETTE, LEO A. ; W.A. BENJAMIN.** Principles of Modem Heterocyclic Chemistry. 1968 **[0016]**

- The Chemistry of Heterocyclic Compounds, A series of Monographs. John Wiley & Sons, 1950, vol. 13, 14, 16, 19, 28 **[0016]**
- *J. Am. Chem. Soc.,* 1960, vol. 82, 5566 **[0016]**
- *Angew Chem. Intl. Ed. Engl.,* 1994, vol. 33, 183-186 **[0025]**
- **YAGUCHI et al.** *Jour. of the Nat. Cancer Inst.,* 2006, vol. 98 (8), 545-556 **[0027]**
- McGraw-Hill Dictionary of Chemical Terms. McGraw-Hill Book Company, 1984 **[0036]**
- **ELIEL, E. ; WILEN, S.** Stereochemistry of Organic Compounds. John Wiley & Sons, Inc, 1994 **[0036]**
- **T. W. GREENE.** Protective Groups in Organic Synthesis. John Wiley & Sons, 1991 **[0043]**
- Remington's Pharmaceutical Sciences. Mack Publishing Company, 1975 **[0144]**