

IMIDAZO[4,5-C]PYRIDINE AND PYRROLO[2,3-C]PYRIDINE DERIVATIVES AS SSAO INHIBITORS

FIELD OF THE INVENTION

The present invention relates to compounds which are inhibitors of SSAO activity. The invention also relates to pharmaceutical compositions comprising these compounds and to the use of these compounds in the treatment or prevention of medical conditions wherein inhibition of SSAO activity is beneficial, such as inflammatory diseases, immune disorders and the inhibition of tumour growth.

BACKGROUND ART

Semicarbazide-sensitive amine oxidase (SSAO) activity is an enzyme activity expressed by Vascular Adhesion Protein-1 (VAP-1) or Amine Oxidase, Copper Containing 3 (AOC3), belongs to the copper-containing amine oxidase family of enzymes (EC.1.4.3.6). Therefore inhibitors of the SSAO enzyme may also modulate the biological functions of the VAP-1 protein. Members of this enzyme family are sensitive to inhibition by semicarbazide and utilize cupric ion and protein-derived topa quinone (TPQ) cofactor in the oxidative deamination of primary amines to aldehydes, hydrogen peroxide, and ammonia according to the following reaction:



Known substrates for human SSAO include endogenous methylamine and aminoacetone as well as some xenobiotic amines such as benzylamine [Lyles, *Int. J. Biochem. Cell Biol.* **1996**, 28, 259-274; Klinman, *Biochim. Biophys. Acta* **2003**, 1647(1-2), 131-137; Mátyus et al., *Curr. Med. Chem.* **2004**, 11(10), 1285-1298; O'Sullivan et al., *Neurotoxicology* **2004**, 25(1-2), 303-315]. In analogy with other copper-containing amine oxidases, DNA-sequence analysis and structure determination suggest that the tissue-bound human SSAO is a homodimeric glycoprotein consisting of two 90–100 kDa subunits anchored to the plasma membrane by a single N-terminal membrane spanning domain [Morris et al., *J. Biol. Chem.* **1997**, 272, 9388-9392; Smith et al., *J. Exp. Med.* **1998**, 188, 17-27; Airene et al., *Protein Science* **2005**, 14, 1964-1974; Jakobsson et al., *Acta Crystallogr. D Biol. Crystallogr.* **2005**, 61(Pt 11), 1550-1562].

SSAO activity has been found in a variety of tissues including vascular and non-vascular smooth muscle tissue, endothelium, and adipose tissue [Lewinsohn, *Braz. J. Med. Biol. Res.* **1984**, 17, 223-256; Nakos & Gossrau, *Folia Histochem. Cytobiol.* **1994**, 32, 3-10; Yu et al., *Biochem. Pharmacol.* **1994**, 47, 1055-1059;

Castillo et al., *Neurochem. Int.* **1998**, 33, 415-423; Lyles & Pino, *J. Neural. Transm. Suppl.* **1998**, 52, 239-250; Jaakkola et al., *Am. J. Pathol.* **1999**, 155, 1953-1965; Morin et al., *J. Pharmacol. Exp. Ther.* **2001**, 297, 563-572; Salmi & Jalkanen, *Trends Immunol.* **2001**, 22, 211-216]. In addition, SSAO protein is found in blood
5 plasma and this soluble form appears to have similar properties as the tissue-bound form [Yu et al., *Biochem. Pharmacol.* **1994**, 47, 1055-1059; Kurkijärvi et al., *J. Immunol.* **1998**, 161, 1549-1557]. It has recently been shown that circulating human and rodent SSAO originates from the tissue-bound form [Göktürk et al., *Am. J. Pathol.* **2003**, 163(5), 1921-1928; Abella et al., *Diabetologia* **2004**, 47(3), 429-438;
10 Stolen et al., *Circ. Res.* **2004**, 95(1), 50-57], whereas in other mammals the plasma/serum SSAO is also encoded by a separate gene called AOC4 [Schwelberger, *J. Neural. Transm.* **2007**, 114(6), 757-762].

The precise physiological role of this abundant enzyme has yet to be fully determined, but it appears that SSAO and its reaction products may have several
15 functions in cell signalling and regulation. For example, recent findings suggest that SSAO plays a role in both GLUT4-mediated glucose uptake [Enrique-Tarancon et al., *J. Biol. Chem.* **1998**, 273, 8025-8032; Morin et al., *J. Pharmacol. Exp. Ther.* **2001**, 297, 563-572] and adipocyte differentiation [Fontana et al., *Biochem. J.* **2001**, 356, 769-777; Mercier et al., *Biochem. J.* **2001**, 358, 335-342]. In addition, SSAO
20 has been shown to be involved in inflammatory processes where it acts as an adhesion protein for leukocytes [Salmi & Jalkanen, *Trends Immunol.* **2001**, 22, 211-216; Salmi & Jalkanen, in "Adhesion Molecules: Functions and Inhibition" K. Ley (Ed.), **2007**, pp. 237-251], and might also play a role in connective tissue matrix development and maintenance [Langford et al., *Cardiovasc. Toxicol.* **2002**, 2(2),
25 141-150; Göktürk et al., *Am. J. Pathol.* **2003**, 163(5), 1921-1928]. Moreover, a link between SSAO and angiogenesis has recently been discovered [Noda et al., *FASEB J.* **2008**, 22(8), 2928-2935], and based on this link it is expected that inhibitors of SSAO have an anti-angiogenic effect.

Several studies in humans have demonstrated that SSAO activity in blood
30 plasma is elevated in conditions such as congestive heart failure, diabetes mellitus, Alzheimer's disease, and inflammation [Lewinsohn, *Braz. J. Med. Biol. Res.* **1984**, 17, 223-256; Boomsma et al., *Cardiovasc. Res.* **1997**, 33, 387-391; Ekblom, *Pharmacol. Res.* **1998**, 37, 87-92; Kurkijärvi et al., *J. Immunol.* **1998**, 161, 1549-

1557; Boomsma et al., *Diabetologia* **1999**, 42, 233–237; Meszaros et al., *Eur. J. Drug Metab. Pharmacokinet.* **1999**, 24, 299–302; Yu et al., *Biochim. Biophys. Acta* **2003**, 1647(1–2), 193–199; Mátyus et al., *Curr. Med. Chem.* **2004**, 11(10), 1285–1298; O'Sullivan et al., *Neurotoxicology* **2004**, 25(1–2), 303–315; del Mar Hernandez et al., *Neurosci. Lett.* **2005**, 384(1–2), 183–187]. The mechanisms underlying these alterations of enzyme activity are not clear. It has been suggested that reactive aldehydes and hydrogen peroxide produced by endogenous amine oxidases contribute to the progression of cardiovascular diseases, diabetic complications and Alzheimer's disease [Callingham et al., *Prog. Brain Res.* **1995**, 106, 305–321; Ekblom, *Pharmacol. Res.* **1998**, 37, 87–92; Yu et al., *Biochim. Biophys. Acta* **2003**, 1647(1–2), 193–199; Jiang et al., *Neuropathol Appl Neurobiol.* **2008**, 34(2), 194–204]. Furthermore, the enzymatic activity of SSAO is involved in the leukocyte extravasation process at sites of inflammation where SSAO has been shown to be strongly expressed on the vascular endothelium [Salmi et al., *Immunity* **2001**, 14(3), 265–276; Salmi & Jalkanen, in “*Adhesion Molecules: Functions and Inhibition*” K. Ley (Ed.), **2007**, pp. 237–251]. Accordingly, inhibition of SSAO has been suggested to have a therapeutic value in the prevention of diabetic complications and in inflammatory diseases [Ekblom, *Pharmacol. Res.* **1998**, 37, 87–92; Salmi et al., *Immunity* **2001**, 14(3), 265–276; Salter-Cid et al., *J. Pharmacol. Exp. Ther.* **2005**, 315(2), 553–562].

WO2007146188 teaches that blocking SSAO activity inhibits leucocyte recruitment, reduces the inflammatory response, and is expected to be beneficial in prevention and treatment of seizures, for example, in epilepsy.

O'Rourke et al (J Neural Transm. 2007;114(6):845–9) examined the potential of SSAO inhibitors in neurological diseases, having previously demonstrated the efficacy of SSAO inhibition in a rat model of stroke. An SSAO inhibitor is tested on relapsing-remitting experimental autoimmune encephalomyelitis (EAE), a mouse model that shares many characteristics with human multiple sclerosis. The data demonstrates the potential clinical benefit of small molecule anti-SSAO therapy in this model and therefore in treatment of human multiple sclerosis.

SSAO knockout animals are phenotypically overtly normal but exhibit a marked decrease in the inflammatory responses evoked in response to various inflammatory stimuli [Stolen et al., *Immunity* **2005**, 22(1), 105–115]. In addition,

antagonism of its function in wild type animals in multiple animal models of human disease (e.g. carrageenan-induced paw inflammation, oxazolone-induced colitis, lipopolysaccharide-induced lung inflammation, collagen-induced arthritis, endotoxin-induced uveitis) by the use of antibodies and/or small molecules has been shown to

5 be protective in decreasing the leukocyte infiltration, reducing the severity of the disease phenotype and reducing levels of inflammatory cytokines and chemokines [Kirton et al., *Eur. J. Immunol.* **2005**, 35(11), 3119-3130; Salter-Cid et al., *J. Pharmacol. Exp. Ther.* **2005**, 315(2), 553-562; McDonald et al., *Annual Reports in Medicinal Chemistry* **2007**, 42, 229-243; Salmi & Jalkanen, in "Adhesion Molecules: Functions and Inhibition" K. Ley (Ed.), **2007**, pp. 237-251; Noda et al., *FASEB J.* **2008** 22(4), 1094-1103; Noda et al., *FASEB J.* **2008**, 22(8), 2928-2935]. This anti-inflammatory protection seems to be afforded across a wide range of inflammatory models all with independent causative mechanisms, rather than being restricted to one particular disease or disease model. This would suggest that SSAO may be a

15 key nodal point for the regulation of the inflammatory response, and it is therefore likely that SSAO inhibitors will be effective anti-inflammatory drugs in a wide range of human diseases. VAP-1 has also been implicated in the progression and maintenance of fibrotic diseases including those of the liver and lung. Weston and Adams (J Neural Transm. **2011**, 118(7), 1055-64) have summarised the

20 experimental data implicating VAP-1 in liver fibrosis, and Weston et al (EASL Poster 2010) reported that blockade of VAP-1 accelerated the resolution of carbon tetrachloride induced fibrosis. In addition VAP-1 has been implicated in inflammation of the lung (e.g. Singh et al., **2003**, Virchows Arch 442:491-495) suggesting that VAP-1 blockers would reduce lung inflammation and thus be of

25 benefit to the treatment of cystic fibrosis by treating both the pro-fibrotic and pro-inflammatory aspects of the disease.

SSAO (VAP-1) is up regulated in gastric cancer and has been identified in the tumour vasculature of human melanoma, hepatoma and head and neck tumours (Yoong KF, McNab G, Hubscher SG, Adams DH. (1998), *J Immunol* **160**, 3978-88.;

30 Irjala H, Salmi M, Alanen K, Gre'nman R, Jalkanen S (2001), *Immunol.* **166**, 6937-6943; Forster-Horvath C, Dome B, Paku S, et al. (2004), *Melanoma Res.* **14**, 135-40.). One report (Marttila-Ichihara F, Castermans K, Auvinen K, Oude Egbrink MG, Jalkanen S, Griffioen AW, Salmi M. (2010), *J Immunol.* **184**, 3164-3173.) has shown

that mice bearing enzymically inactive VAP-1 grow melanomas more slowly, and have reduced tumour blood vessel number and diameter. The reduced growth of these tumours was also reflected in the reduced (by 60-70%) infiltration of myeloid suppressor cells. Encouragingly VAP-1 deficiency had no effect on vessel or lymph
5 formation in normal tissue.

Small molecules of different structural classes have previously been disclosed as SSAO inhibitors, for example in WO 02/38153 (tetrahydroimidazo[4,5-c]pyridine derivatives), in WO 03/006003 (2-indanylhrazine derivatives), in WO 2005/014530 (allylhrazine and hydroxylamine (aminooxy) compounds) and in WO 2007/120528
10 (allylamino compounds). Additional SSAO inhibitors are disclosed in PCT/EP2009/062011 and PCT/EP2009/062018. Additional SSAO inhibitors are disclosed in PCT/GB2012/052265.

Patent application PCT/US2012/066153 (published as WO2013/078254) discloses compounds apparently useful as inhibitors of serine/threonine protein
15 kinases. The compounds are structurally related to the claimed compounds, and have a bicyclic heteroaryl ring system substituted with a phenyl-cyclobutaneamine substituent.

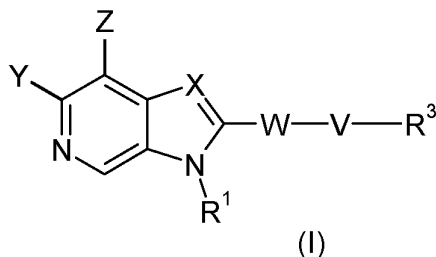
The invention described here relates to a new class of SSAO inhibitors with biological, pharmacological, and pharmacokinetic characteristics that make them
20 suitable for use as prophylactic or therapeutic agents in a wide range of human inflammatory diseases and immune disorders. This therapeutic capacity is designed to block SSAO enzyme action, reducing the levels of pro-inflammatory enzyme products (aldehydes, hydrogen peroxide and ammonia) whilst also decreasing the adhesive capacity of immune cells and correspondingly their activation and final
25 extra-vasation. Diseases where such an activity is expected to be therapeutically beneficial include all diseases where immune cells play a prominent role in the initiation, maintenance or resolution of the pathology, such as multiple sclerosis, arthritis and vasculitis.

Detailed Description of the Invention

30 It has surprisingly been found that the compounds of formula (I) below are inhibitors of SSAO. They are therefore useful for the treatment or prevention of diseases in which inhibition of SSAO activity is beneficial, such as inflammation,

inflammatory diseases, immune or autoimmune disorders, and inhibition of tumour growth.

According to a first aspect of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt, or N-oxide thereof:



5

Wherein:

Y is selected from hydrogen, hydroxyl, -NH₂, -NH-C₁₋₄-alkyl, -NH-halo-C₁₋₄-alkyl, or -C₁₋₄-alkoxy;

Z is selected from hydrogen, halogen, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, C₁₋₄-alkoxy, halo-C₁₋₄-alkoxy, -CONH₂, -SO₂NH₂, -NH₂, -NHC₁₋₄-alkyl, or -NHhalo-C₁₋₄-alkyl;

R¹ is a phenyl ring, or a 5 or 6-membered heteroaryl ring, either ring being optionally substituted with one or more substituents selected from halogen, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, a 3-7 membered cycloalkyl ring, -OR⁵, -NR^{4A}R^{4B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, and -NR⁶S(O)₂R⁵; wherein

R^{4A}, R^{4B}, R⁵ and R⁶ are each independently selected from hydrogen, C₁₋₄-alkyl or halo-C₁₋₄-alkyl, or

R^{4A} and R^{4B} together with the nitrogen to which they are attached form a 3-7 membered cyclic amino group, optionally substituted by one or more substituents selected from: halogen, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, C₁₋₄-alkoxy, halo-C₁₋₄-alkoxy, -CONH₂, -SO₂NH₂, -NH₂, -NHC₁₋₄-alkyl, -NHhalo-C₁₋₄-alkyl;

X is selected from -N= or -C(R²)=;

R² is selected from hydrogen, halogen, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{4A}R^{4B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, -SO₂R⁵, -SO₂NR^{4A}R^{4B} and -NR⁶S(O)₂R⁵;

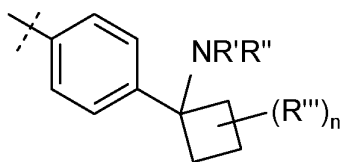
W is a phenyl ring or a 5 or 6-membered heteroaryl ring, either ring being optionally substituted with one or more substituents selected from halogen, cyano,

oxo C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{7A}R^{7B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{7A}R^{7B}, -C(O)NR^{7A}R^{7B}, -C(O)R⁵, -C(O)OR⁵, -SO₂R⁵, -SO₂NR^{7A}R^{7B} and -NR⁶S(O)₂R⁵;

R^{7A} and R^{7B} are independently hydrogen, C₁₋₄-alkyl or halo-C₁₋₄-alkyl.

- 5 V is selected from a bond, -O-, -N(R⁶)-, -(C=O)-, -CONR⁶-, -NR⁶C(O)-, or -C₁₋₄-alkylene-, wherein the C₁₋₄-alkylene group is optionally substituted by halogen, and wherein any one of the carbon atoms of the C₁₋₄-alkylene group may be replaced by -O- or -N(R⁶)-;

- R³ is selected from hydrogen, -C₁₋₄-alkyl, -C₁₋₄-alkyl-C₁₋₄-alkoxy or a 3-7
 10 membered heterocyclic ring or 3-7 membered cycloalkyl ring, or a 5 or 6-membered heteroaryl ring, any one of the rings being optionally substituted with one or more substituents selected from halogen, oxo, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{4A}R^{4B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, -SO₂R⁵, -SO₂NR^{4A}R^{4B} and -NR⁶S(O)₂R⁵;
 15 with the proviso that groups -WVR³ and/or R¹ are not:



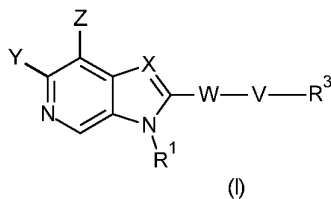
wherein

n is 0, 1, or 2;

- R' and R'' are independently selected from the group consisting of H, -C₁-C₆alkyl, -
 20 (C=O)-C₁-C₆ alkyl and -(C=O)OC(CH₃)₃; and
 R''' is H, OH, or C₁-C₆ alkyl.

And according to a second aspect of the invention there is provided a compound of
 formula (I) or a pharmaceutically acceptable salt, or N-oxide thereof

25



Wherein:

Y is selected from hydrogen, hydroxyl, -NH₂, -NH-C₁₋₄-alkyl, -NH-halo-C₁₋₄-alkyl, or -C₁₋₄-alkoxy;

Z is selected from hydrogen, halogen, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, C₁₋₄-alkoxy, halo-C₁₋₄-alkoxy, -CONH₂, -SO₂NH₂, -NH₂, -NHC₁₋₄-alkyl, or -NHhalo-C₁₋₄-alkyl;

R¹ is a phenyl ring, or a 5 or 6-membered heteroaryl ring, either ring being optionally substituted with one or more substituents selected from halogen, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{4A}R^{4B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, and -NR⁶S(O)₂R⁵; wherein

R^{4A}, R^{4B}, R⁵ and R⁶ are each independently selected from hydrogen, C₁₋₄-alkyl or halo-C₁₋₄-alkyl, or

R^{4A} and R^{4B} together with the nitrogen to which they are attached form a 3-7 membered cyclic amino group, optionally substituted by one or more substituents selected from: halogen, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, C₁₋₄-alkoxy, halo-C₁₋₄-alkoxy, -CONH₂, -SO₂NH₂, -NH₂, -NHC₁₋₄-alkyl, -NHhalo-C₁₋₄-alkyl;

X is selected from -N= or -C(R²)=;

R² is selected from hydrogen, halogen, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{4A}R^{4B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, -SO₂R⁵, -SO₂NR^{4A}R^{4B} and -NR⁶S(O)₂R⁵;

W is a phenyl ring or a 5 or 6-membered heteroaryl ring, either ring being optionally substituted with one or more substituents selected from halogen, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{7A}R^{7B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{7A}R^{7B}, -C(O)NR^{7A}R^{7B}, -C(O)R⁵, -C(O)OR⁵, -SO₂R⁵, -SO₂NR^{7A}R^{7B} and -NR⁶S(O)₂R⁵;

R^{7A} and R^{7B} are independently hydrogen, C₁₋₄-alkyl or halo-C₁₋₄-alkyl.

V is selected from a bond, -O-, -N(R⁶)-, -(C=O)-, -CONR⁶-, -NR⁶C(O)-, or -C₁₋₄-alkylene-, wherein the C₁₋₄-alkylene group is optionally substituted by halogen, and wherein any one of the carbon atoms of the C₁₋₄-alkylene group may be replaced by -O- or -N(R⁶)-;

R³ is hydrogen or a 3-7 membered heterocyclic ring or 3-7 membered cycloalkyl ring selected from cyclopropyl, cyclopentyl or cyclohexyl, or a 5 or 6-

membered heteroaryl ring, any one of the rings being optionally substituted with one or more substituents selected from halogen, oxo, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{4A}R^{4B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, -SO₂R⁵, -SO₂NR^{4A}R^{4B} and -NR⁶S(O)₂R⁵.

In addition to the surprising activity of the compounds of formula (I) at the SSAO receptor, it has been surprisingly found that the claimed compounds have surprisingly low activity at the hERG ion channel. The person skilled in the art, for example a medicinal chemist, understands that low hERG activity is an important property for a pharmaceutical drug compound. Without wishing to be bound by theory, it is believed that the -WVR³ group as defined in claim 1 is especially advantageous in relation to reduced hERG activity.

It is expected that compounds of the invention may be prepared in the form of hydrates, and solvates. Any reference herein, including the claims herein, to "compounds with which the invention is concerned" or "compounds of the invention" or "the present compounds", and the like, includes reference to salts, hydrates, and solvates of such compounds. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Individual compounds of the invention may exist in an amorphous form and /or several polymorphic forms and may be obtained in different crystal habits. Any reference herein, including the claims herein, to "compounds with which the invention is concerned" or "compounds of the invention" or "the present compounds", and the like, includes reference to the compounds irrespective of amorphous or polymorphic form.

Since compounds of the invention have a nitrogen atom in an aromatic ring they may form N-oxides, and the invention includes compounds of the invention in their N-oxide form.

DEFINITIONS

The following definitions shall apply throughout the specification and the appended claims, unless otherwise stated or indicated.

The term "C₁₋₄-alkyl" denotes a straight or branched alkyl group having from 1 to 4 carbon atoms. For parts of the range C₁₋₄-alkyl all subgroups thereof are contemplated such as C₁₋₃-alkyl, C₁₋₂-alkyl, C₂₋₄-alkyl, C₂₋₃-alkyl and C₃₋₄-alkyl. Examples of said C₁₋₄-alkyl include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl and *tert*-butyl.

Unless otherwise specified, the term "C₃₋₇-cycloalkyl" refers to a monocyclic saturated or partially unsaturated hydrocarbon ring system having from 3 to 7 carbon atoms. Examples of said C₃₋₇-cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cycloheptenyl. For parts of the range "C₃₋₇-cycloalkyl" all subgroups thereof are contemplated such as C₃₋₇-cycloalkyl, C₃₋₆-cycloalkyl, C₃₋₅-cycloalkyl, C₃₋₄-cycloalkyl, C₄₋₇-cycloalkyl, C₄₋₆-cycloalkyl, C₄₋₅-cycloalkyl, C₅₋₇-cycloalkyl, C₅₋₆-cycloalkyl, and C₆₋₇-cycloalkyl.

The term "C₁₋₄-alkoxy" refers to a straight or branched C₁₋₄-alkyl group which is attached to the remainder of the molecule through an oxygen atom. For parts of the range C₁₋₄-alkoxy, all subgroups thereof are contemplated such as C₁₋₃-alkoxy, C₁₋₂-alkoxy, C₂₋₄-alkoxy, C₂₋₃-alkoxy and C₃₋₄-alkoxy. Examples of said C₁₋₄-alkoxy include methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy and *tert*-butoxy.

The term "haloC₁₋₄-alkoxy" refers to a straight or branched C₁₋₄-alkyl group which is attached to the remainder of the molecule through an oxygen atom and has one or more hydrogen atoms thereof replaced with halogen such as fluoro or chloro. For parts of the range C₁₋₄-alkoxy, all subgroups thereof are contemplated. Examples of said C₁₋₄-alkoxy include trifluoromethoxy.

The term "hydroxy-C₁₋₄-alkyl" denotes a straight or branched C₁₋₄-alkyl group that has one or more hydrogen atoms thereof replaced with OH. Examples of said hydroxy-C₁₋₄-alkyl include hydroxymethyl, 2-hydroxyethyl and 2,3-dihydroxypropyl.

The term "halo-C₁₋₄-alkyl" denotes a straight or branched C₁₋₄-alkyl group that has one or more hydrogen atoms thereof replaced with halogen. Examples of said halo-C₁₋₄-alkyl include fluoromethyl, trifluoromethyl, trichloromethyl and 2-fluoroethyl.

The term "cyano-C₁₋₄-alkyl" denotes a straight or branched C₁₋₄-alkyl group that has one or more hydrogen atoms thereof replaced with cyano. Examples of said cyano-C₁₋₄-alkyl include cyanomethyl, 2-cyanoethyl and 3-cyanopropyl.

The term "amino-C₁₋₄-alkyl" denotes a straight or branched C₁₋₄-alkyl group substituted with an amino group. Examples of said amino-C₁₋₄-alkyl group include aminomethyl and 2-aminoethyl.

5 The term "C₁₋₄-alkylamino-C₁₋₄-alkyl" denotes an amino-C₁₋₄-alkyl group as defined above, wherein the amino group is substituted with a straight or branched C₁₋₄-alkyl group. Examples of said C₁₋₄-alkylamino-C₁₋₄-alkyl include methylaminoethyl and ethylaminopropyl.

10 The term "di(C₁₋₄-alkyl)amino-C₁₋₄-alkyl" denotes an amino-C₁₋₄-alkyl group as defined above, wherein the amino group is disubstituted with straight or branched C₁₋₄-alkyl groups, which can be the same or different. Examples of said di(C₁₋₄-alkyl)amino-C₁₋₄-alkyl include *N,N*-dimethylaminomethyl, *N*-ethyl-*N*-methylaminoethyl and *N,N*-diethylaminomethyl.

15 The terms "heteroaryl" and "heteroaromatic ring" denote a monocyclic heteroaromatic ring comprising 5 to 6 ring atoms in which one or more of the ring atoms are other than carbon, such as nitrogen, sulphur or oxygen. Examples of heteroaryl groups include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, tetrazolyl, pyrazolyl, pyridazinyl, pyrazinyl and thiadiazolyl.

20 The terms "heterocyclyl" and "heterocyclic ring" denote a non-aromatic, fully saturated or partially unsaturated, preferably fully saturated, monocyclic ring system having from 3 to 7 ring atoms, especially 5 or 6 ring atoms, in which one or more of the ring atoms are other than carbon, such as nitrogen, sulphur or oxygen. Examples of heterocyclic groups include piperidinyl, morpholinyl, homomorpholinyl, azepanyl, piperazinyl, oxo-piperazinyl, diazepinyl, tetrahydropyridinyl, tetrahydropyranyl, pyrrolidinyl, tetrahydrofuranlyl, and dihydropyrrolyl, groups.

25 The term "heterocyclic-C₁₋₄-alkyl" refers to a heterocyclic ring that is directly linked to a straight or branched C₁₋₄-alkyl group via a carbon or nitrogen atom of said ring. Examples of said heterocyclic-C₁₋₄-alkyl include piperidin-4-ylmethyl, piperidin-1-ylmethyl, morpholin-4-yl-methyl and piperazin-4-ylmethyl. The C₁₋₄-alkyl part, which includes methylene, ethylene, propylene or butylene, is optionally substituted by one or more substituents selected from halogen, amino, methoxy, or hydroxyl.

The term "C₁₋₄-alkylene" denotes a straight or branched divalent saturated hydrocarbon chain having from 1 to 4 carbon atoms. The C₁₋₄-alkylene chain may be

attached to the rest of the molecule and to the radical group through one carbon within the chain or through any two carbons within the chain. Examples of C₁₋₄-alkylene radicals include methylene [-CH₂-], 1,2-ethylene [-CH₂-CH₂-], 1,1-ethylene [-CH(CH₃)-], 1,2-propylene [-CH₂-CH(CH₃)-] and 1,3-propylene [-CH₂-CH₂-CH₂-].

- 5 When referring to a "C₁₋₄-alkylene" radical, all subgroups thereof are contemplated, such as C₁₋₂-alkylene, C₂₋₃-alkylene, or C₃₋₄-alkylene.

"Halogen" refers to fluorine, chlorine, bromine or iodine, preferably fluorine and chlorine, most preferably fluorine.

"Hydroxy" refers to the -OH radical.

- 10 "Cyano" refers to the -CN radical.

"Oxo" refers to the carbonyl group =O.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

- 15 "Pharmaceutically acceptable" means being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

- "Treatment" as used herein includes prophylaxis of the named disorder or
20 condition, or amelioration or elimination of the disorder once it has been established.

"An effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect).

- 25 "Prodrugs" refers to compounds that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. A prodrug may be inactive when administered to a subject in need thereof, but is converted *in vivo* to an active compound of the invention. Prodrugs are typically rapidly transformed *in vivo* to yield the parent compound of the invention, *e.g.* by
30 hydrolysis in the blood. The prodrug compound usually offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see Silverman, R. B., *The Organic Chemistry of Drug Design and Drug Action*, 2nd Ed., Elsevier Academic Press (2004), pp. 498-549). Prodrugs of a compound of the

invention may be prepared by modifying functional groups, such as a hydroxy, amino or mercapto groups, present in a compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound of the invention. Examples of prodrugs include, but are not limited to, acetate, formate and succinate derivatives of hydroxy functional groups or phenyl carbamate derivatives of amino functional groups.

Throughout the specification and the appended claims, a given chemical formula or name shall also encompass all salts, hydrates, solvates, N-oxides and prodrug forms thereof. Further, a given chemical formula or name shall encompass all tautomeric and stereoisomeric forms thereof. Tautomers include enol and keto forms. Stereoisomers include enantiomers and diastereomers. Enantiomers can be present in their pure forms, or as racemic (equal) or unequal mixtures of two enantiomers. Diastereomers can be present in their pure forms, or as mixtures of diastereomers. Diastereomers also include geometrical isomers, which can be present in their pure *cis* or *trans* forms or as mixtures of those.

The compounds of formula (I) may be used as such or, where appropriate, as pharmacologically acceptable salts (acid or base addition salts) thereof. The pharmacologically acceptable addition salts mentioned below are meant to comprise the therapeutically active non-toxic acid and base addition salt forms that the compounds are able to form. Compounds that have basic properties can be converted to their pharmaceutically acceptable acid addition salts by treating the base form with an appropriate acid. Exemplary acids include inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulphuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propanoic acid, hydroxyacetic acid, lactic acid, pyruvic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, benzenesulphonic acid, toluenesulphonic acid, methanesulphonic acid, trifluoroacetic acid, fumaric acid, succinic acid, malic acid, tartaric acid, citric acid, salicylic acid, *p*-aminosalicylic acid, pamoic acid, benzoic acid, ascorbic acid and the like. Exemplary base addition salt forms are the sodium, potassium, calcium salts, and salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, and amino acids, such as, e.g. arginine and lysine. The term addition salt as used herein also comprises solvates which the compounds and

salts thereof are able to form, such as, for example, hydrates, alcoholates and the like.

The Group Y

In an embodiment Y is from hydrogen, hydroxyl, -NH₂, -NH-C₁₋₄-alkyl such as
 5 -NH-Methyl, -NH-ethyl, or -NH-isopropyl, -NH-halo-C₁₋₄-alkyl such as -NHtrifluoromethyl, or -C₁₋₄-alkoxy such as methoxy. In an embodiment Y is hydrogen.

The Group Z

In an embodiment Z is hydrogen, halogen such as fluoro or chloro, hydroxyl,
 10 cyano, C₁₋₄-alkyl such as methyl or isopropyl, halo-C₁₋₄-alkyl such as trifluoromethyl, C₁₋₄-alkoxy such as methoxy, halo-C₁₋₄-alkoxy such as trifluoromethoxy, -CONH₂, -SO₂NH₂, -NH₂, -NHC₁₋₄-alkyl such as -NH-Methyl, -NH-ethyl, or -NH-isopropyl, or -NHhalo-C₁₋₄-alkyl. In an embodiment Z is hydrogen.

The Group R¹

In an R¹ embodiment is a phenyl ring, or a 5 or 6-membered heteroaryl ring
 15 either ring being optionally substituted with one or more substituents selected from halogen such as fluoro or chloro, cyano, C₁₋₄-alkyl such as methyl or isopropyl, halo-C₁₋₄-alkyl such as trifluoromethyl, cyano-C₁₋₄-alkyl such as methylcyano, -OR⁵ such as methoxy or trifluoromethoxy, -NR^{4A}R^{4B} such as -NH₂, -NHMethyl, -NHisopropyl, -
 20 NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵ such as -COCH₃, -C(O)OR⁵, and -NR⁶S(O)₂R⁵. In an embodiment R¹ is optionally substituted phenyl, pyridyl, pyrrole, furan, imidazole, or thiophene.

In an embodiment R¹ is a phenyl ring, or a 5 or 6-membered heteroaryl ring
 25 substituted with a 3-7 membered cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; preferably cyclopropyl.

R^{4A}, R^{4B}, R⁵ and R⁶ are each independently selected from hydrogen, C₁₋₄-alkyl
 such as methyl, ethyl or isopropyl, or halo-C₁₋₄-alkyl such as trifluoromethyl, or

R^{4A} and R^{4B} together with the nitrogen to which they are attached form a 3-7
 30 membered cyclic amino group such as aziridine, azetidine, oxetane, pyrrolidine, piperidine, piperazine, homopiperidine, homopiperazine, morpholine, or tetrahydrofuran, optionally substituted by one or more substituents selected from: halogen such as fluoro or chloro, hydroxyl, cyano, C₁₋₄-alkyl such as methyl or isopropyl, halo-C₁₋₄-alkyl such as trifluoromethyl, C₁₋₄-alkoxy such as methoxy, halo-

C₁₋₄-alkoxy such as trifluoromethoxy, -CONH₂, -SO₂NH₂, -NH₂, -NHC₁₋₄-alkyl, -NHhalo-C₁₋₄-alkyl;

The Group X

In an embodiment X is selected from -N= or -C(R²)=;

5 The Group R²

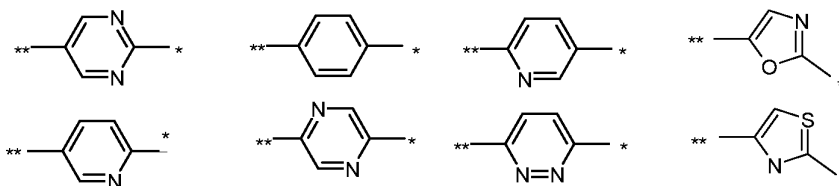
In an embodiment R² is hydrogen, halogen such as fluoro or chloro, cyano, C₁₋₄-alkyl such as methyl or ethyl or isopropyl, halo-C₁₋₄-alkyl such as trifluoromethyl. In an embodiment R² is hydrogen.

The Group W

- 10 In an embodiment W is a phenyl ring. In an alternative embodiment W a 6-membered heterocyclic ring selected from pyridine, pyridazine, pyrazine, or pyrimidine. In an alternative embodiment W is a 5-membered ring selected from oxazole, thiazole or imidazole. In an embodiment W is imidazolyl and the imidazolyl ring is connected to the pyrrolopyridine core (i.e. the rest of the molecule) via an
- 15 imidazolyl ring carbon atom. In an embodiment W is a pyrazole ring.

Any of the aforementioned rings are optionally substituted with one or more substituents as defined in claim 1. In an embodiment W is substituted with one or more groups selected from fluoro, chloro, cyano, methyl or trifluoromethyl.

- In an embodiment W is a divalent group selected from any one of the following
- 20 rings, any of which rings is optionally substituted with one or more substituents as defined in relation to formula (I).



wherein the bond marked ** is directly connected to the rest of the molecule and the atom marked * is directly connected to V.

25

The Group V

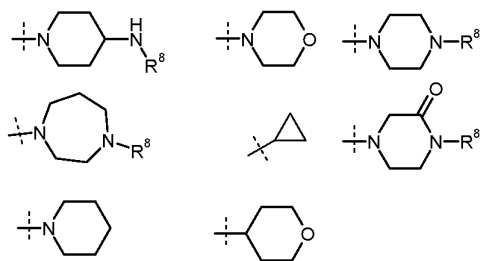
In an embodiment V is selected from a bond, -O-, -N(R⁶)- such as -NH- or -N(CH₃)-, -(C=O)-, -CONR⁶- such as -CONH- or -CON(CH₃)-, -NR⁶C(O)- such as -NHC(O)- or -N(CH₃)C(O)-, or -C₁₋₄-alkylene-, wherein the C₁₋₄-alkylene group is

optionally substituted by halogen such as fluoro or chloro, and wherein any one of the carbon atoms of the C₁₋₄-alkylene group may be replaced by -O- or -N(R⁶)- such as -CH₂O- in either direction or -CH₂-NH-; -CH₂-N(CH₃)- in either direction.

The Group R³

- 5 In an embodiment R³ is hydrogen. In an alternative embodiment R³ is an optionally substituted 3-7 membered heterocyclic ring such as aziridine, azetidine, oxetane, pyrrolidine, piperidine, piperazine, homopiperidine, homopiperazine, morpholine, or tetrahydrofuran. In an embodiment R³ is an optionally substituted 3-7 membered cycloalkyl ring such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
- 10 In an alternative embodiment R³ is an optionally substituted 5 or 6-membered heteroaryl ring such as imidazole, phenyl, pyridine, thophene. The optional substituents are defined in formula (I). In an embodiment any one of the rings is optionally substituted with one or more substituents selected from halogen such as fluoro or chloro, oxo, hydroxyl, cyano, C₁₋₄-alkyl such as methyl, ethyl, propyl, t-butyl,
- 15 or isopropyl, halo-C₁₋₄-alkyl such as trifluoromethyl, cyano-C₁₋₄-alkyl, -OR⁵ such as methoxy or trifluoromethoxy, -NR^{4A}R^{4B} such as -NH₂, NHmethyl, or morpholine or piperidine, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, -SO₂R⁵, -SO₂NR^{4A}R^{4B} and -NR⁶S(O)₂R⁵.

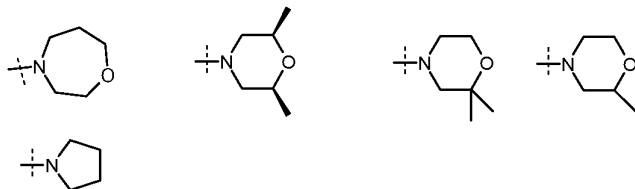
In an embodiment R³ is selected from the following ring systems:



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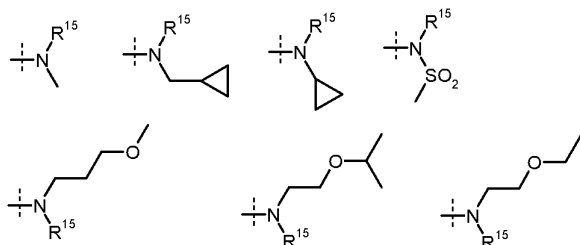
Wherein R⁸ is selected from hydrogen, CH₃, -CONH₂, -NHCONH₂, -S(O)₂CH₃, -COCH₃.

In an embodiment R³ is selected from the following ring systems:



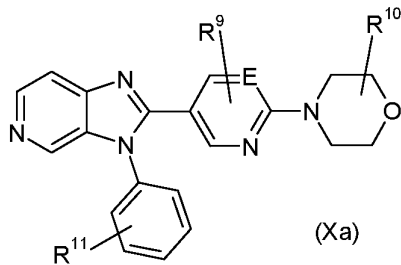
In an embodiment R^3 is selected from hydrogen, $-C_{1-4}$ -alkyl such as methyl, ethyl, propyl and isopropyl, and $-C_{1-4}$ -alkyl- C_{1-4} -alkoxy such as $-(CH_2)_2OCH_3$.

In an embodiment the group $-VR^3$ is selected from:



5 wherein R^{15} is hydrogen or methyl.

In an embodiment, the invention includes a compound of formula (Xa)



wherein E is $-C=$ or $-N=$,

R^9 and R^{10} are each independently one or more substituents selected from
 10 hydrogen, halogen, cyano, oxo, C_{1-4} -alkyl such as methyl, $-OC_{1-4}$ -alkyl such as OCH_3 , and halo- C_{1-4} -alkyl; and

R^{11} is one or more substituents selected from hydrogen, halogen such as fluoro and/or chloro, cyano, cyclopropyl, C_{1-4} -alkyl such as methyl, and halo- C_{1-4} -alkyl.

In one aspect, the invention relates to a compound of formula (I) for use in
 15 therapy. The compounds as defined above are useful as inhibitors of SSAO activity. As such, they are useful in the treatment or prevention of conditions and diseases in which inhibition of SSAO activity is beneficial. More specifically, they are useful for the treatment or prevention of inflammation, inflammatory diseases, immune or autoimmune disorders, cystic fibrosis, or inhibition of tumour growth; and they are
 20 useful in the manufacture of a medicament for treatment or prevention of inflammation, inflammatory diseases, immune or autoimmune disorders, cystic fibrosis, or inhibition of tumour growth

In particular, it is believed that compounds of formula (I) are useful for the treatment or prevention of arthritis (such as rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis and psoriatic arthritis), synovitis, vasculitis, conditions associated with inflammation of the bowel (such as Crohn's disease, ulcerative colitis, inflammatory bowel disease and irritable bowel syndrome), atherosclerosis, multiple sclerosis, Alzheimer's disease, vascular dementia, pulmonary inflammatory diseases (such as asthma, chronic obstructive pulmonary disease and acute respiratory distress syndrome), fibrotic diseases (including idiopathic pulmonary fibrosis, cardiac fibrosis and systemic sclerosis (scleroderma)), inflammatory diseases of the skin (such as contact dermatitis, atopic dermatitis and psoriasis), systemic inflammatory response syndrome, sepsis, inflammatory and/or autoimmune conditions of the liver (such as autoimmune hepatitis, primary biliary cirrhosis, alcoholic liver disease, sclerosing cholangitis, and autoimmune cholangitis), diabetes (type I or II) and/or the complications thereof, chronic heart failure, congestive heart failure, ischemic diseases (such as stroke and ischemia-reperfusion injury), and myocardial infarction and/or the complications thereof, or epilepsy.

It is believed that the compounds of the invention are especially useful for the treatment or prevention of vasculitis, including, but not limited to, giant cell arteritis, Takayasu's arteritis, Polyarteritis nodosa, Kawasaki disease, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, cryoglobulinemia, cutaneous leukocytoclastic angiitis and primary angiitis of the central nervous system.

It is also believed that the compounds of the invention are especially useful for the treatment of rheumatoid arthritis, chronic obstructive pulmonary disease or atopic dermatitis.

In view of the evidence cited in the above introduction that VAP-1 is up regulated in several cancers, including gastric cancer, melanoma, hepatoma and head and neck tumours and that mice bearing enzymatically inactive VAP-1 grow melanomas more slowly, and in view of the link between VAP-1 and angiogenesis, it is also expected that the compounds of the invention are anti-angiogenic and therefore have utility in the treatment of cancers by inhibition of tumour growth.

The invention thus includes the compounds of formula (I) above for use in the treatment or prevention of the above-mentioned conditions and diseases. The invention also includes the use of said compounds in the manufacture of a medicament for the treatment or prevention of the above-mentioned conditions and diseases. The invention furthermore includes methods for treatment or prevention of such conditions and diseases, comprising administering to a mammal, including man, in need of such treatment an effective amount of a compound as defined above.

Methods delineated herein include those wherein the subject is identified as in need of a particular stated treatment. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

In other aspects, the methods herein include those further comprising monitoring subject response to the treatment administrations. Such monitoring may include periodic sampling of subject tissue, fluids, specimens, cells, proteins, chemical markers, genetic materials, etc. as markers or indicators of the treatment regimen. In other methods, the subject is prescreened or identified as in need of such treatment by assessment for a relevant marker or indicator of suitability for such treatment.

In one embodiment, the invention provides a method of monitoring treatment progress. The method includes the step of determining a level of diagnostic marker (Marker) (e.g., any target or cell type delineated herein modulated by a compound herein) or diagnostic measurement (e.g., screen, assay) in a subject suffering from or susceptible to a disorder or symptoms thereof delineated herein, in which the subject has been administered a therapeutic amount of a compound herein sufficient to treat the disease or symptoms thereof. The level of Marker determined in the method can be compared to known levels of Marker in either healthy normal controls or in other afflicted patients to establish the subject's disease status. In preferred embodiments, a second level of Marker in the subject is determined at a time point later than the determination of the first level, and the two levels are compared to monitor the course of disease or the efficacy of the therapy. In certain preferred embodiments, a pre-treatment level of Marker in the subject is determined

prior to beginning treatment according to this invention; this pre-treatment level of Marker can then be compared to the level of Marker in the subject after the treatment commences, to determine the efficacy of the treatment.

In certain method embodiments, a level of Marker or Marker activity in a subject is determined at least once. Comparison of Marker levels, e.g., to another measurement of Marker level obtained previously or subsequently from the same patient, another patient, or a normal subject, may be useful in determining whether therapy according to the invention is having the desired effect, and thereby permitting adjustment of dosage levels as appropriate. Determination of Marker levels may be performed using any suitable sampling/expression assay method known in the art or described herein. Preferably, a tissue or fluid sample is first removed from a subject. Examples of suitable samples include blood, urine, tissue, mouth or cheek cells, and hair samples containing roots. Other suitable samples would be known to the person skilled in the art. Determination of protein levels and/or mRNA levels (e.g., Marker levels) in the sample can be performed using any suitable technique known in the art, including, but not limited to, enzyme immunoassay, ELISA, radiolabeling/assay techniques, blotting/chemiluminescence methods, real-time PCR, and the like.

COMPOSITIONS

A currently preferred embodiment of the invention is a pharmaceutical composition comprising a compound of formula (I), together with one or more pharmaceutically acceptable carriers and/or excipients.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for various modes of administration. It will be appreciated that compounds of the invention may be administered together with a physiologically acceptable carrier, excipient, or diluent. The pharmaceutical compositions of the invention may be administered by any suitable route, preferably by oral, rectal, nasal, topical (including buccal and sublingual), sublingual, transdermal, intrathecal, transmucosal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration.

Other formulations may conveniently be presented in unit dosage form, e.g., tablets and sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. Pharmaceutical formulations are

usually prepared by mixing the active substance, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutically acceptable carriers, diluents or excipients. Examples of excipients are water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such formulations may also contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like. Usually, the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and more preferably between 1-50% by weight in preparations for oral administration.

The formulations can be further prepared by known methods such as granulation, compression, microencapsulation, spray coating, etc. The formulations may be prepared by conventional methods in the dosage form of tablets, capsules, granules, powders, syrups, suspensions, suppositories or injections. Liquid formulations may be prepared by dissolving or suspending the active substance in water or other suitable vehicles. Tablets and granules may be coated in a conventional manner. To maintain therapeutically effective plasma concentrations for extended periods of time, compounds of the invention may be incorporated into slow release formulations.

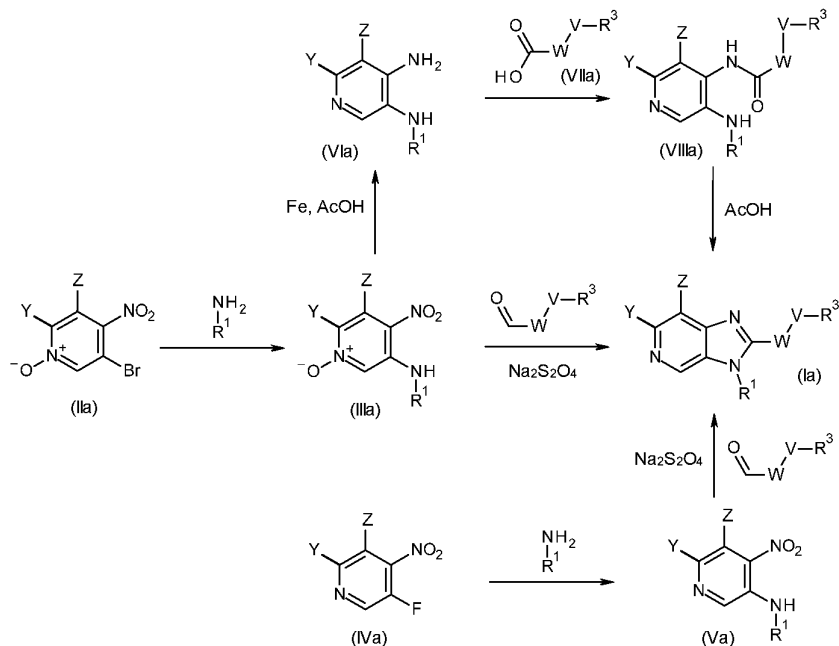
The dose level and frequency of dosage of the specific compound will vary depending on a variety of factors including the potency of the specific compound employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 100 mg per kilo of body weight, administered singly or multiply in doses, e.g. from about 0.01 mg to about 25 mg each. Normally, such a dosage is given orally but parenteral administration may also be chosen.

30 PREPARATION OF COMPOUNDS OF THE INVENTION

The compounds of formula (I) above may be prepared by, or in analogy with, conventional methods. The preparation of intermediates and compounds according to the examples of the present invention may in particular be illuminated by the

following Schemes. Definitions of variables in the structures in schemes herein are commensurate with those of corresponding positions in the formulas delineated herein.

Scheme 1. General synthetic routes for preparation of compounds of formula (I) wherein X is N (i.e. compounds of general formula (Ia))



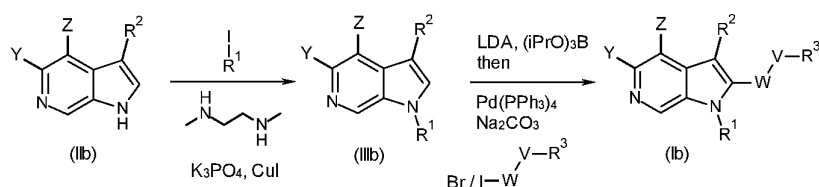
wherein V, W, X, Y, Z, R¹, R² and R³ are as defined in formula (I);

Compounds of general formula (I) where X is N (designated compounds of general formula (Ia)), can easily be prepared by a number of alternative routes. For example, 3-bromo-4-nitropyridine N-oxides of general formula (IIa) can undergo SnAr displacement with R¹NH₂ amines to give compounds of general formula (IIIa), which can in turn be reductively cyclised to give compounds of general formula (Ia). Alternatively, 3-fluoro-4-nitropyridines of general formula (IVa) can undergo SnAr displacement with R¹NH₂ amines to give compounds of general formula (Va), which can in turn be reductively cyclised to give compounds of general formula (Ia). Alternatively, compounds of general formula (IIIa) can be reduced to pyridine-3,4-diamines of general formula (VIa). Compounds of general formula (VIa) can then undergo amide formation with carboxylic acids of general formula (VIIa) to give amides of general formula (VIIIa) which can be cyclised to give compounds of general formula (Ia).

Optionally, the group W-V-R³ can be built up sequentially using standard chemistry methodologies including amide, urea and sulphonamide formation. If required, standard protecting group strategies can be employed to facilitate the synthesis.

- 5 Optionally, a compound of formula (Ia) can also be transformed into another compound of formula (Ia) in one or more synthetic steps.

Scheme 2. General synthetic routes for preparation of compounds of formula (I) wherein X is CR² (i.e. compounds of general formula (Ib))



- 10 wherein V, W, X, Y, Z, R¹, R² and R³ are as defined in formula (I);

- Compounds of general formula (I) where X is CR² (designated compounds of general formula (Ib)), can easily be prepared standard means. For example, 6-azaindoles of general formula (IIb) can be N-arylated with R¹-I iodides to give compounds of general formula (IIIb) which can in turn be converted to compounds of general formula (Ib) by boronate formation and subsequent Suzuki coupling.
- 15

Optionally, the group W-V-R³ can be built up sequentially using standard chemistry methodologies including amide, urea and sulphonamide formation. If required, standard protecting group strategies can be employed to facilitate the synthesis.

- 20 Optionally, a compound of formula (Ib) can also be transformed into another compound of formula (Ib) in one or more synthetic steps.

The following abbreviations have been used:

Ac	acetyl
aq	aqueous
Boc	<i>tertiary</i> -butyloxycarbonyl
calcd	calculated
d	day(s)
DCM	dichloromethane

DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N</i> -ethylcarbodiimide
ES ⁺	electrospray ionization
Et ₃ N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
Ex	Example
h	hour(s)
HATU	O-(7-azabenzotriazol-1-yl)- <i>N,N,N,N</i> -tetramethyluronium hexafluorophosphate
HBTU	O-benzotriazole- <i>N,N,N,N</i> -tetramethyl-uronium-hexafluoro phosphate
HPLC	High Performance Liquid Chromatography
Int	Intermediate
LCMS	Liquid Chromatography Mass Spectrometry
LDA	Lithium diisopropylamide
M	molar
MeCN	acetonitrile
MeOH	methanol
[MH] ⁺	protonated molecular ion
Min	minute(s)
NMP	1-methyl-2-pyrrolidinone
QTOF	Quadrupole time-of-flight mass spectrometer
RP	reverse phase
RT	room temperature
Rt	retention time
sat	saturated
TFA	trifluoroacetic acid
THF	Tetrahydrofuran

UV	Ultra violet
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

EXAMPLES AND INTERMEDIATE COMPOUNDS

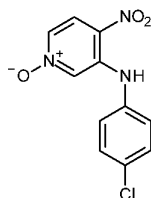
Experimental Methods

Reactions were conducted at room temperature unless otherwise specified.

- 5 Microwave reactions were performed with a Biotage microwave reactor using process vials fitted with aluminium caps and septa. Preparative chromatography was performed using a Flash Master Personal system equipped with Isolute Flash II silica columns or using a CombiFlash Companion system equipped with GraceResolv silica column. Reverse Phase HPLC was performed on a Gilson
- 10 system with a UV detector equipped with Phenomenex Synergi Hydro RP 150x10mm, or YMC ODS-A 100/150x20mm columns. The purest fractions were collected, concentrated and dried under vacuum. Compounds were typically dried in a vacuum oven at 40°C prior to purity analysis. Compound analysis was performed by HPLC/LCMS using an Agilent 1100 HPLC system / Waters ZQ mass
- 15 spectrometer connected to an Agilent 1100 HPLC system with a Phenomenex Synergi, RP-Hydro column (150x4.6mm, 4um, 1.5mL per min, 30°C, gradient 5-100% MeCN (+0.085% TFA) in water (+0.1% TFA) over 7min, 200-300nm). Accurate masses were measured using a Waters QTOF electrospray ion source and corrected using Leucine Enkephalin lockmass. Spectra were acquired in positive
- 20 and negative electrospray mode. The acquired mass range was m/z 100-1000. Test compounds were dissolved in DMSO to give a 10mM stock solution. Typically 5mL of the DMSO stock were diluted with 495mL of acetonitrile and then further diluted with acetonitrile and water (1:1) to give a final concentration of 0.2mM. The mass values reported correspond either to the parent molecule with a hydrogen added
- 25 [MH] or with a hydrogen subtracted [M-H]. The compounds prepared were named using IUPAC nomenclature.

INTERMEDIATE 1

3-[(4-Chlorophenyl)amino]-4-nitropyridin-1-ium-1-olate

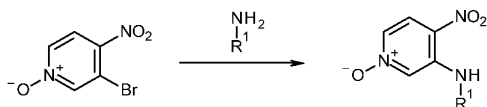


3-Bromo-4-nitropyridine *N*-oxide (1.00g, 4.57mmol) and 4-chloroaniline (1.75g, 13.7mmol) were dissolved in EtOH and heated at 60°C for 18h. The reaction mixture was cooled to 0°C and the precipitate was collected by filtration and washed with cold EtOH to give the title compound as an orange solid (317mg, 26.1%). LCMS (ES⁺): 266.1 [MH]⁺. HPLC: Rt 5.44min, 99.5% purity.

INTERMEDIATES 2-3

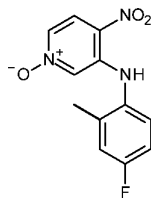
Intermediates 2-3 were prepared similarly to Intermediate 1, by coupling of 3-bromo-4-nitropyridine *N*-oxide with the appropriate aniline; see Table 1 below.

Table 1: SnAr formation of anilines



Int	Structure	Name	Form, Yield, LCMS, HPLC
2		3-[(4-Fluorophenyl)amino]-4-nitropyridin-1-ium-1-olate	Orange solid Yield 2.66g, 46.7% LCMS (ES ⁺): 250.1 [MH] ⁺ HPLC: Rt 5.00min, 97.3% purity
3		3-[(2-Fluoro-4-methylphenyl)amino]-4-nitropyridin-1-ium-1-olate	Orange solid Yield 200mg, 5.55% LCMS (ES ⁺): 264.0 [MH] ⁺ HPLC: Rt 5.52min, 93.2% purity

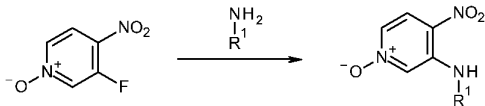
INTERMEDIATE 4

3-[(4-Fluoro-2-methylphenyl)amino]-4-nitropyridin-1-ium-1-olate

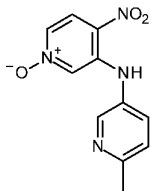
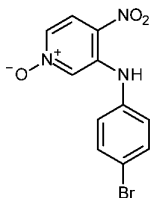
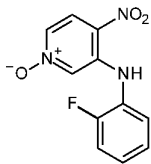
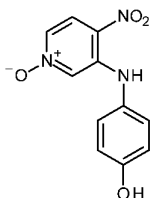
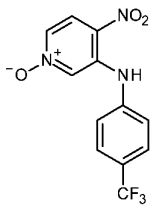
- 3-Fluoro-4-nitropyridine *N*-oxide (1.00g, 6.33mmol) and 4-fluoro-2-methylaniline (2.42mL, 25.3mmol) were dissolved in EtOH (12mL) and heated at 90°C for 16h.
- 5 The reaction mixture was cooled to RT, the precipitate was collected by filtration and washed with cold EtOH (10mL) to give the title compound (1.60g, 96.2%) as a yellow solid. LCMS (ES⁺): 264.1 [MH]⁺. HPLC: Rt 5.56min, 95.9% purity.

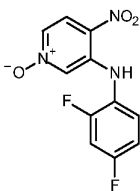
INTERMEDIATES 5-12

- 10 Intermediates 5-12 were prepared similarly to Intermediate 4, by coupling of 3-fluoro-4-nitropyridine *N*-oxide with the appropriate aniline; see Table 2 below.

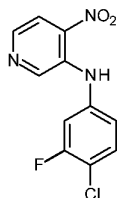
Table 2: SnAr formation of anilines

Int	Structure	Name	Form, Yield, LCMS, HPLC
5		3-[(2-Chloro-4-fluorophenyl)amino]-4-nitropyridin-1-ium-1-olate	Yellow solid Yield 1.93g, 53.9% LCMS (ES ⁺): 284.2 [MH] ⁺ HPLC: Rt 5.67min, 96.0% purity
6		3-[(4-Methylphenyl)amino]-4-nitropyridin-1-ium-1-olate	Orange solid Yield 1.12g, 96.2% LCMS (ES ⁺): 246.1 [MH] ⁺ HPLC: Rt 5.65min, 99.3% purity

7		3-[(6-Methylpyridin-3-yl)amino]-4-nitropyridin-1-ium-1-olate	Orange solid Yield 1.04g, 89.0% LCMS (ES ⁺): 247.0 [MH] ⁺ HPLC: Rt 2.86min, 64.5% purity
8		3-[(4-Bromophenyl)amino]-4-nitropyridin-1-ium-1-olate	Orange solid Yield 1.55g, crude LCMS (ES ⁺): 309.9 [MH] ⁺ HPLC: Rt 5.66min, 95.8% purity
9		3-[(2-Fluorophenyl)amino]-4-nitropyridin-1-ium-1-olate	Orange solid Yield 1.08g, 91.3% LCMS (ES ⁺): 250.0 [MH] ⁺ HPLC: Rt 5.14min, 100% purity
10		3-[(4-Hydroxyphenyl)amino]-4-nitropyridin-1-ium-1-olate	Dark orange solid Yield 1.40g, crude LCMS (ES ⁺): 248.0 [MH] ⁺ HPLC: Rt 4.25min, 96.8% purity
11		4-Nitro-3-[[4-(trifluoromethyl)phenyl]amino]pyridin-1-ium-1-olate	Orange solid Yield 1.38g, 97.3% LCMS (ES ⁺): 300.0 [MH] ⁺ HPLC: Rt 5.84min, 93.8% purity

12		3-[(2,4-Difluorophenyl)amino]-4-nitropyridin-1-ium-1-olate	Yellow solid Yield 2.16g, 63.9% LCMS (ES ⁺): 268.0 [MH] ⁺ HPLC: Rt 5.14min, 99.3% purity
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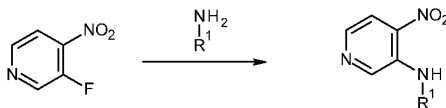
INTERMEDIATE 13

N-(4-Chloro-3-fluorophenyl)-4-nitropyridin-3-amine

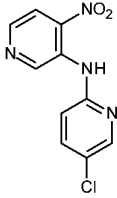
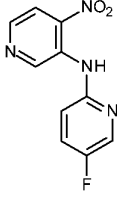
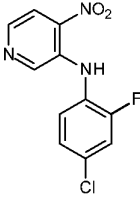
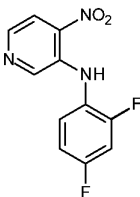
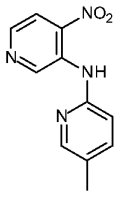
- 5 NaH (422mg, 60% dispersion in mineral oil, 10.6mmol) was suspended in THF (20mL) and 4-chloro-3-fluoroaniline (1.54g, 10.6mmol) and 3-fluoro-4-nitropyridine (500mg, 3.52mmol) were added. The reaction mixture was stirred for 18h, quenched with sat. aq. NH₄Cl (2mL), and concentrated *in vacuo*. The residue was partitioned between water (50mL) and DCM (50mL) and the organic fraction was dried
- 10 (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (207mg, 22.0%) as an orange solid. LCMS (ES⁺): 268.0 [MH]⁺.

INTERMEDIATES 14-18

- 15 Intermediates 14-18 were prepared similarly to Intermediate 13, by coupling of 3-fluoro-4-nitropyridine with the appropriate aniline; see Table 3 below.

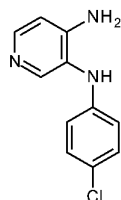
Table 3: S_NAr formation of anilines

Int	Structure	Name	Form, Yield, LCMS, HPLC
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14		<i>N</i> -(5-Chloropyridin-2-yl)-4-nitropyridin-3-amine	Orange gum Yield 221mg, 25.1% LCMS (ES ⁺): 251.1 [MH] ⁺ HPLC: Rt 5.99min, 93.6% purity
15		5-Fluoro- <i>N</i> -(4-nitropyridin-3-yl)pyridin-2-amine	Orange solid Yield 441mg, 53.5% LCMS (ES ⁺): 235.0 [MH] ⁺ HPLC: Rt 5.40min, 95.2% purity
16		<i>N</i> -(4-Chloro-2-fluorophenyl)-4-nitropyridin-3-amine	Orange solid Yield 1.26g, 66.9% LCMS (ES ⁺): 268.1 [MH] ⁺
17		<i>N</i> -(2,4-Difluorophenyl)-4-nitropyridin-3-amine	Orange solid Yield 752mg, 42.5% LCMS (ES ⁺): 252.0 [MH] ⁺ HPLC: Rt 5.91min, 77.8% purity
18		5-Methyl- <i>N</i> -(4-nitropyridin-3-yl)pyridin-2-amine	Dark red solid Yield 611mg, 37.7% LCMS (ES ⁺): 231.1 [MH] ⁺ HPLC: Rt 4.61min, 97.5% purity

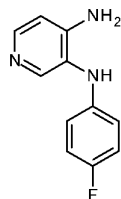
INTERMEDIATE 19

3-*N*-(4-Chlorophenyl)pyridine-3,4-diamine



Intermediate 1 (317mg, 1.19mmol) was dissolved in AcOH (10mL) and iron powder (333mg, 5.97mmol) was added. The reaction mixture was heated at reflux for 1h, diluted with water (50mL), basified with Na₂CO₃ and extracted into DCM (3x50mL).
5 The combined organic fractions were dried (MgSO₄) and concentrated *in vacuo* to give the title compound as a red gum (254mg, 96.9%). LCMS (ES⁺): 220.2 [MH]⁺. HPLC: Rt 4.31min, 99.5% purity.

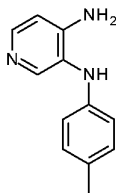
INTERMEDIATE 20

10 **3-N-(4-Fluorophenyl)pyridine-3,4-diamine**

Intermediate 20 was prepared similarly to Intermediate 19, using Intermediate 2 instead of Intermediate 1, to give the title compound (6.33g, 91.3%) as a brown solid. LCMS (ES⁺): 204.1 [MH]⁺.

15

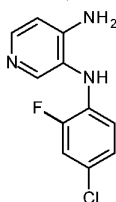
INTERMEDIATE 21

3-N-(4-Methylphenyl)pyridine-3,4-diamine

Intermediate 6 (6.00g, 24.5mmol) and ammonium formate (12.3g, 196mmol) were
20 suspended in EtOH (200mL), Raney Nickel (50% slurry in water; 11.0mL) was added and the reaction mixture was heated at 85°C for 2h, filtered through Celite

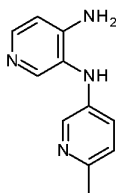
and concentrated *in vacuo*. The residue was partitioned between water (150mL) and DCM/MeOH (150mL/20mL) and the aqueous fraction was extracted with DCM (100mL). The combined organic fractions were dried (MgSO₄) and concentrated *in vacuo* to give the title compound (3.20g, 65.6%) as a blue solid. LCMS (ES⁺): 200.1 [MH]⁺.

INTERMEDIATE 22

3-*N*-(4-Chloro-2-fluorophenyl)pyridine-3,4-diamine

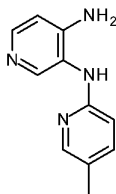
Intermediate 22 was prepared similarly to Intermediate 21, using Intermediate 16 instead of Intermediate 6, to give the title compound (509mg, 31.7%) as an orange solid. LCMS (ES⁺): 238.1 [MH]⁺.

INTERMEDIATE 23

3-*N*-(6-Methylpyridin-3-yl)pyridine-3,4-diamine

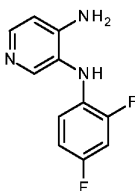
Intermediate 7 (1.40g, 5.69mmol) and hydrazine monohydrate (1.11mL, 22.8mmol) were suspended in THF (20mL) and EtOH (20mL), Raney nickel (~50% slurry in water; 2mL) was added slowly at 0°C and the reaction mixture was warmed to RT and stirred for 2h. The mixture was filtered through Celite washing with MeOH (80mL) and the combined filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (836mg, 73.4%) as an off white solid. LCMS (ES⁺): 201.1 [MH]⁺.

INTERMEDIATE 24

3-*N*-(5-Methylpyridin-2-yl)pyridine-3,4-diamine

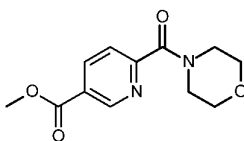
Intermediate 24 was prepared similarly to Intermediate 23, using Intermediate 18 instead of Intermediate 7, to give the title compound (741mg, 70.1%) as a pale
5 purple solid. LCMS (ES^+): 201.1 $[\text{MH}]^+$. HPLC: Rt 2.39min, 98.5% purity.

INTERMEDIATE 25

3-*N*-(2,4-Difluorophenyl)pyridine-3,4-diamine

10 Intermediate 25 was prepared similarly to Intermediate 23, using Intermediate 12 instead of Intermediate 7, to give the title compound (1.32g, 73.6%) as a pink solid. LCMS (ES^+): 222.0 $[\text{MH}]^+$. HPLC: Rt 4.08min, 99.2% purity.

INTERMEDIATE 26

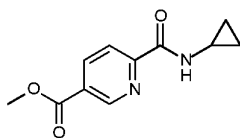
15 Methyl 6-[(morpholin-4-yl)carbonyl]pyridine-3-carboxylate

5-(Methoxycarbonyl)pyridine-2-carboxylic acid (758mg, 4.18mmol) was dissolved in DMF (25mL) and morpholine (603uL, 5.23mmol), Et_3N (2.45mL, 16.7mmol) and HBTU (1.67g, 4.39mmol) were added. The reaction mixture was stirred for 16h and
20 concentrated *in vacuo*. The residue was dissolved in EtOAc (100mL), washed with sat. aq. Na_2CO_3 (100mL), dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (914mg, 87.3%)

as a yellow oil. LCMS (ES^+): 251.2 $[MH]^+$.

INTERMEDIATE 27

Methyl 6-(cyclopropylcarbamoyl)pyridine-3-carboxylate

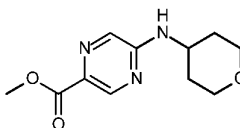


5

Intermediate 27 was prepared similarly to Intermediate 26, using cyclopropylamine instead of morpholine, to give the title compound (774mg, 42.4%) as a white solid. LCMS (ES^+): 221.2 $[MH]^+$.

10 INTERMEDIATE 28

Methyl 5-[(oxan-4-yl)amino]pyrazine-2-carboxylate

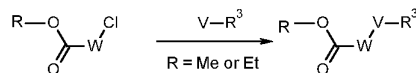


Methyl 5-chloro-2-pyrazinecarboxylate (507mg, 2.94mmol), Et_3N (1.08mL, 7.64mmol) and 4-aminotetrahydropyran (395uL, 3.82mmol) were dissolved in dioxane (5mL) and heated in a microwave reactor at 100°C for 20min. Water (50mL) and brine (25mL) were added and the reaction mixture was extracted into EtOAc (2x100mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (236mg, 33.9%) as a yellow oil. LCMS (ES^+): 238.2 $[MH]^+$.

20 INTERMEDIATES 29-35

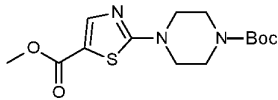
Intermediates 29-35 were prepared similarly to Intermediate 28, by coupling of with the appropriate aromatic ester with the appropriate amine; see Table 4 below.

Table 4: Coupling of with the appropriate aromatic ester with the appropriate amine

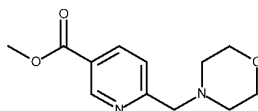


25

Int	Structure	Name	Form, Yield, LCMS, HPLC
29		Methyl 6-(4-(((<i>tert</i> -butoxy)carbonyl)amino)pyrrolidin-1-yl)pyridine-3-carboxylate	Off white solid Yield 1.66g, 84.9% LCMS (ES ⁺): 336.1 [MH] ⁺ HPLC: Rt 4.73min, 98.2% purity.
30		Ethyl 2-[(cyclopropylmethyl)amino]pyrimidine-5-carboxylate	Yellow solid Yield 566mg, 95.5% LCMS (ES ⁺): 222.1 [MH] ⁺ HPLC: Rt 5.79min, 92.9% purity.
31		Ethyl 2-(cyclopropylamino)pyrimidine-5-carboxylate	White solid Yield 526mg, 94.7% LCMS (ES ⁺): 208.1 [MH] ⁺ HPLC: Rt 4.86min, 93.7% purity.
32		Methyl 5-(morpholin-4-yl)pyrazine-2-carboxylate	Pale yellow solid Yield 628mg, 95.8% LCMS (ES ⁺): 224.2 [MH] ⁺
33		<i>tert</i> -Butyl 4-[4-(methoxycarbonyl)-1,3-thiazol-2-yl]piperazine-1-carboxylate	White solid Yield 324mg, 35.1% LCMS (ES ⁺): 350.1 [MNa] ⁺ HPLC: Rt 6.04min, 100% purity.
34		<i>tert</i> -Butyl 4-[5-(methoxycarbonyl)-1,3-oxazol-2-yl]piperazine-1-carboxylate	Pale yellow solid Yield 406mg, 42.1% LCMS (ES ⁺): 334.2 [MNa] ⁺ HPLC: Rt 5.81min, 97.1% purity.

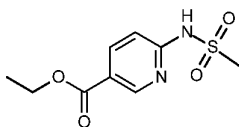
35		<i>tert</i> -Butyl 4-[5-(methoxycarbonyl)-1,3-thiazol-2-yl]piperazine-1-carboxylate	White solid Yield 712mg, 64.4% LCMS (ES ⁺): 350.2 [MNa] ⁺ . HPLC: Rt 6.34min, 99.0% purity.
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INTERMEDIATE 36

Methyl 6-(morpholin-4-ylmethyl)pyridine-3-carboxylate

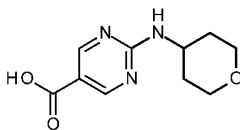
- 5 Methyl 6-formylnicotinate (507mg, 3.07mmol) and morpholine (267uL, 3.07mmol) were dissolved in DCM (20mL) and NaBH(OAc)₃ (976mg, 4.60mmol) was added. The reaction mixture was stirred for 2h. The reaction mixture was diluted with DCM (40mL) then washed with sat. aq. Na₂CO₃ (40mL), dried (MgSO₄) and the solvents removed *in vacuo* to yield the title compound (660mg, 91.0%) as a yellow oil. LCMS (ES⁺): 237.2 [MH]⁺.
- 10

INTERMEDIATE 37

Methyl 6-(cyclopropylcarbamoyl)pyridine-3-carboxylate

- 15 Ethyl 6-aminopyridine-3-carboxylate (738mg, 4.44mmol) was dissolved in pyridine (20mL), cooled to 0°C and methanesulfonyl chloride (1.72mL, 22.2mmol) was added. The reaction mixture was stirred at RT for 16h, concentrated *in vacuo* and partitioned between DCM (50mL) and 1M aq. citric acid (50mL). The organic fraction was dried (MgSO₄) and concentrated *in vacuo* to give the title compound (1.34g, crude) as a brown solid. LCMS (ES⁺): 245.1 [MH]⁺.
- 20

INTERMEDIATE 38

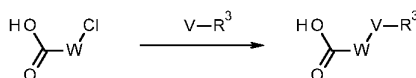
2-[(Oxan-4-yl)amino]pyrimidine-5-carboxylic acid

- 2-Chloropyrimidine-5-carboxylic acid (500mg, 3.15mmol), Et₃N (1.15mL, 8.20mmol) and 4-aminotetrahydropyran (335mg, 3.31mmol) were dissolved in dioxane (10mL) and heated in a microwave reactor at 150°C for 30min. The reaction mixture was concentrated *in vacuo* to give the title compound (701mg, crude) as a beige solid. LCMS (ES⁺): 224.1 [MH]⁺.

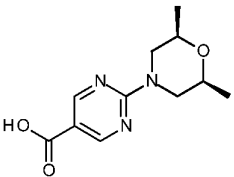
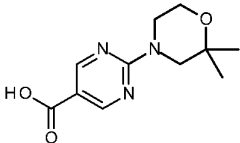
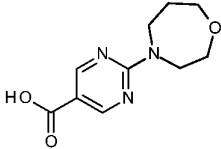
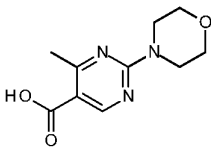
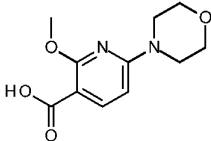
INTERMEDIATES 39-50

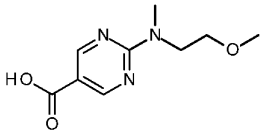
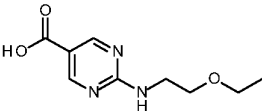
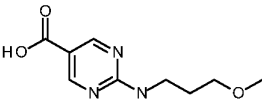
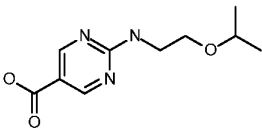
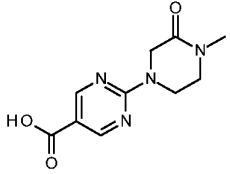
- Intermediates 39-50 were prepared similarly to Intermediate 38, by coupling of with the appropriate carboxylic acid with the appropriate amine; see Table 5 below.

Table 5: Coupling of with the appropriate carboxylic acid with the appropriate amine.

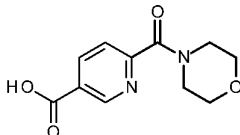


Int	Structure	Name	Form, Yield, LCMS, HPLC
39		2-(3-Oxopiperazin-1-yl)pyrimidine-5-carboxylic acid	Beige solid Yield 701mg, crude LCMS (ES ⁺): 223.0 [MH] ⁺
40		4-Methyl-6-(morpholin-4-yl)pyridine-3-carboxylic acid	Off white solid Yield 401mg, 31.0% LCMS (ES ⁺): 223.1 [MH] ⁺ HPLC: Rt 3.12min, 80.5% purity

41		2-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]pyrimidine-5-carboxylic acid	Yellow gum Yield 750mg, 100% LCMS (ES ⁺): 238.1 [MH] ⁺ HPLC: Rt 4.75min, 96.5% purity
42		2-(2,2-Dimethylmorpholin-4-yl)pyrimidine-5-carboxylic acid	Yellow gum Yield 224mg, 99.8% LCMS (ES ⁺): 238.1 [MH] ⁺ HPLC: Rt 4.57min, 96.2% purity
43		2-(1,4-Oxazepan-4-yl)pyrimidine-5-carboxylic acid	Beige solid Yield 1.50mg, 100% LCMS (ES ⁺): 224.1 [MH] ⁺
44		4-Methyl-2-(morpholin-4-yl)pyrimidine-5-carboxylic acid	Yellow solid Yield 540mg, 83.5% LCMS (ES ⁺): 224.1 [MH] ⁺ HPLC: Rt 4.28min, 98.2% purity
45		2-Methoxy-6-(morpholin-4-yl)pyridine-3-carboxylic acid	White solid Yield 151mg, 23.8% LCMS (ES ⁺): 239.1 [MH] ⁺ HPLC: Rt 4.55min, 84.0% purity

46		2-[(2-methoxyethyl)(methyl)amino]pyrimidine-5-carboxylic acid	Pale orange solid Yield 752mg, crude LCMS (ES ⁺): 212.0 [MH] ⁺ HPLC: Rt 4.10min, 94.9% purity
47		2-[(2-Ethoxyethyl)amino]pyrimidine-5-carboxylic acid	Orange solid Yield 1.34g, crude LCMS (ES ⁺): 212.1 [MH] ⁺ HPLC: Rt 3.84min, 87.0% purity
48		2-[(3-Methoxypropyl)amino]pyrimidine-5-carboxylic acid	Pale yellow solid Yield 758mg, crude LCMS (ES ⁺): 212.1 [MH] ⁺ HPLC: Rt 3.67min, 97.7% purity
49		2-[(2-(Propan-2-yloxy)ethyl)amino]pyrimidine-5-carboxylic acid	Orange solid Yield 1.79g, crude LCMS (ES ⁺): 226.1 [MH] ⁺ HPLC: Rt 4.25min, 98.4% purity
50		2-(4-Methyl-3-oxopiperazin-1-yl)pyrimidine-5-carboxylic acid	White solid Yield 1.95g, 87.0% LCMS (ES ⁺): 237.1 [MH] ⁺ HPLC: Rt 3.63min, 99.8% purity

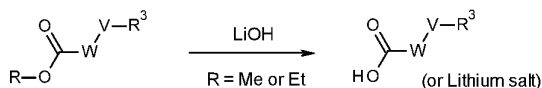
INTERMEDIATE 51

6-[(Morpholin-4-yl)carbonyl]pyridine-3-carboxylic acid

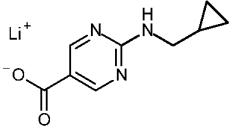
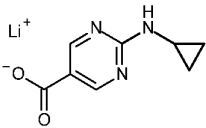
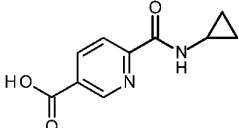
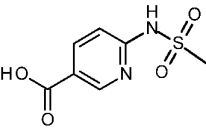
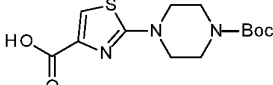
Intermediate 26 (914mg, 3.65mmol) was dissolved in THF/water (24mL, 1:1), lithium
 5 hydroxide monohydrate (184mg, 4.38mmol) was added and the reaction mixture
 was stirred for 20min. 1M aq. HCl (5mL) was added and the reaction mixture was
 extracted with EtOAc (2x100mL), dried (MgSO₄) and concentrated *in vacuo* to give
 the title compound (633mg, 73.4%) as a white solid. LCMS (ES⁺): 237.1 [MH]⁺.

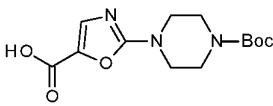
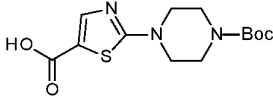
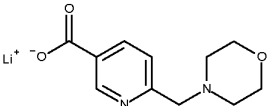
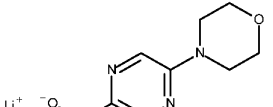
10 INTERMEDIATES 52-62

Intermediates 52-62 were prepared similarly to Intermediate 51, by LiOH mediated
 ester hydrolysis; see Table 6 below.

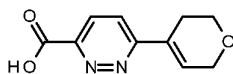
Table 6: Ester hydrolyses

Int	Structure	Name	Intermediate(s), Form, Yield, LCMS, HPLC
52		Lithium 5-[(oxan-4-yl)amino]pyrazine-2-carboxylate	From Intermediate 28 Yellow solid Yield 222mg, 100% LCMS (ES ⁺): 224.1 [MH] ⁺
53		Lithium 6-(4-[(<i>tert</i> -butoxy)carbonyl] amino)piperidin-1-yl)pyridine-3-carboxylate	From Intermediate 29 White solid Used crude LCMS (ES ⁺): 322.1 [MH] ⁺ HPLC: Rt 4.20min, 96.8% purity

54		Lithium 2-[(cyclopropylmethyl) amino] pyrimidine-5-carboxylate	From Intermediate 30 Off white solid Used crude LCMS (ES ⁺): 194.1 [MH] ⁺ HPLC: Rt 4.09min, 97.4% purity
55		Lithium (cyclopropylamino) pyrimidine-5-carboxylate	From Intermediate 31 Off white solid Used crude LCMS (ES ⁺): 180.1 [MH] ⁺ HPLC: Rt 3.23min, 100% purity
56		6-(Cyclopropylcarbamoyl) pyridine-3-carboxylic acid	From Intermediate 27 Pink solid Yield 559mg, 77.1% LCMS (ES ⁺): 207.1 [MH] ⁺
57		6-Methanesulfonamido pyridine-3-carboxylic acid	From Intermediate 37 Beige solid Yield 737mg, 76.4% LCMS (ES ⁺): 217.0 [MH] ⁺
58		2-{4-[(<i>tert</i> -Butoxy)carbonyl] piperazin-1-yl}-1,3-thiazole-4-carboxylic acid	From Intermediate 33 White solid Yield 275mg, 88.7% LCMS (ES ⁺): 336.1 [MNa] ⁺ HPLC: Rt 5.12min, 100% purity

59		2-{4-[(<i>tert</i> -Butoxy)carbonyl]piperazin-1-yl}-1,3-oxazole-5-carboxylic acid	From Intermediate 34 White solid Yield 324mg, 84.4% LCMS (ES ⁺): 320.1 [MNa] ⁺ HPLC: Rt 4.77min, 100% purity
60		2-{4-[(<i>tert</i> -Butoxy)carbonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid	From Intermediate 35 White solid Yield 656mg, 97.9% LCMS (ES ⁺): 336.1 [MNa] ⁺ HPLC: Rt 5.19min, 99.3% purity
61		Lithium 6-(morpholin-4-yl)methylpyridine-3-carboxylate	From Intermediate 36 Yellow solid Used crude LCMS (ES ⁺): 223.1 [MH] ⁺
62		Lithium 5-(morpholin-4-yl)pyrazine-2-carboxylate	From Intermediate 32 Yellow solid Used crude LCMS (ES ⁺): 210.1 [MH] ⁺

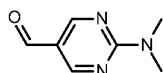
INTERMEDIATE 63

6-(3,6-Dihydro-2H-pyran-4-yl)pyridazine-3-carboxylic acid

- 5 Methyl 6-chloropyridazine-3-carboxylate (1.00g, 5.79mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran (1.22g, 5.79mmol), Pd(PPh₃)₄ (536mg, 0.464mmol) and Cs₂CO₃ (3.40g, 10.4mmol) were suspended in dioxane (8mL) and water (8mL) and heated in a microwave reactor at 125°C for 30min. 1M

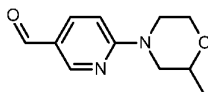
aq. HCl (10mL) was added, the precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was passed through a silica pad eluting with 30% MeOH in DCM and concentrated *in vacuo* to give the title compound as a white solid (946mg, 79.2%). LCMS (ES⁺): 207.1 [MH]⁺. HPLC: Rt 3.30min, 49.9%
5 purity.

INTERMEDIATE 64

2-(Dimethylamino)pyrimidine-5-carbaldehyde

10 2-Chloropyrimidine-5-carbaldehyde (412mg, 2.89mmol) and Et₃N (482uL, 3.47mmol) were dissolved in dioxane (20mL) and a solution of Me₂NH in THF (1.59mL, 2.0M, 3.18mmol) was added. The reaction mixture was stirred for 1h, filtered, washed with dioxane (5mL), and concentrated *in vacuo* to give the title compound (427mg, 97.7%) as a yellow solid. LCMS (ES⁺): 152.2 [MH]⁺. HPLC: Rt
15 4.14min, 97.9% purity.

INTERMEDIATE 65

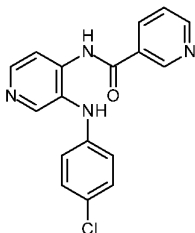
6-(2-Methylmorpholin-4-yl)pyridine-3-carbaldehyde

20 2-Chloro-5-pyridinecarboxaldehyde (500mg, 3.53mmol) and 2-methylmorpholine (750mg, 7.42mmol) were dissolved in DMF (2mL) and the reaction mixture was heated at 100°C in a microwave reactor for 20min and concentrated *in vacuo*. The residue was suspended in dioxane (5mL), filtered and concentrated *in vacuo* to give the title compound (730mg, 100%) as an orange gum. LCMS (ES⁺): 207.1 [MH]⁺.

25

INTERMEDIATE 66

N-{3-[(4-Chlorophenyl)amino]pyridin-4-yl}pyridine-3-carboxamide

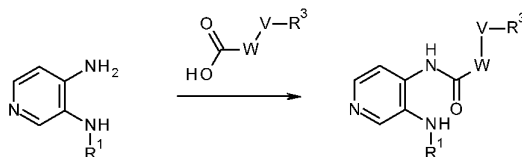


Intermediate 19 (234mg, 1.07mmol), pyridine-4-carboxylic acid (393mg, 3.20mmol) and DIPEA (741uL, 4.26mmol) were dissolved in DMF (10mL) and EDC (613mg, 3.20mmol) was added. The reaction mixture was stirred for 18h and further pyridine-3-carboxylic acid (393mg, 3.20mmol) and EDC (613mg, 3.20mmol) were added. The reaction mixture was stirred for 5h, diluted with 1M aq. Na₂CO₃ (50mL) and extracted into DCM (3x50mL). The combined organic fractions were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound as a red gum (297mg, 85.8%). LCMS (ES⁺): 325.1 [MH]⁺. HPLC: Rt 4.08min, 99.0% purity.

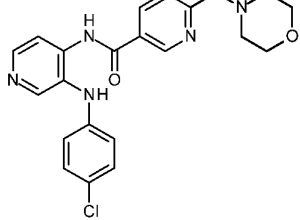
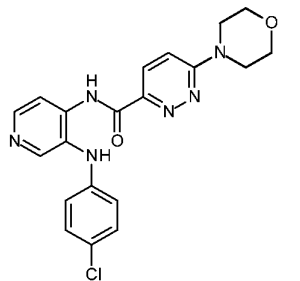
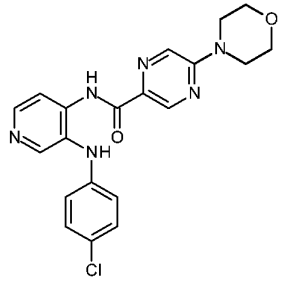
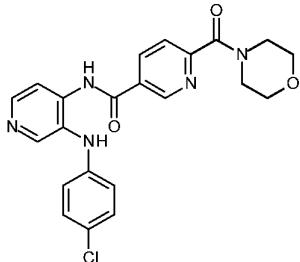
INTERMEDIATES 67-123

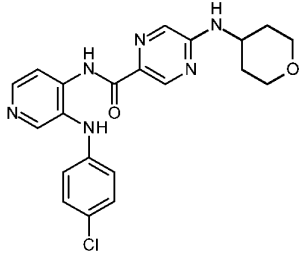
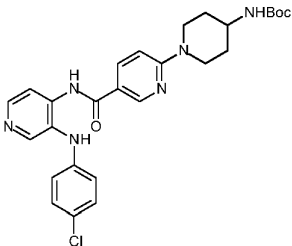
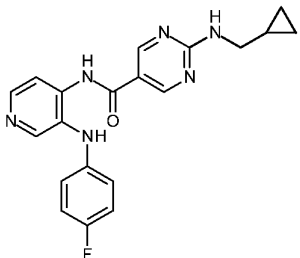
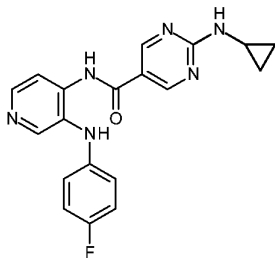
Intermediates 67-123 were prepared similarly to Intermediate 66, by coupling of Intermediates 19-25 with the appropriate carboxylic acid; see Table 7 below.

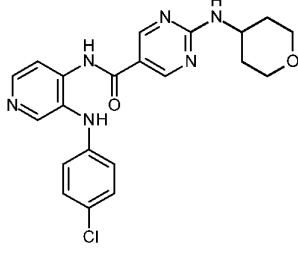
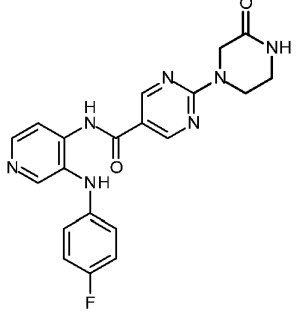
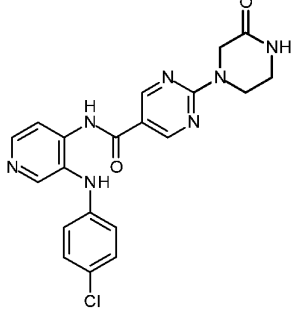
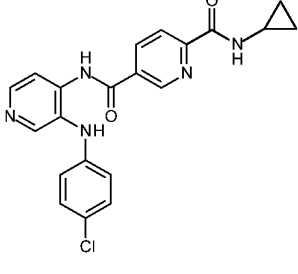
Table 7: Amide couplings

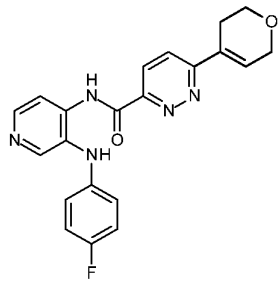
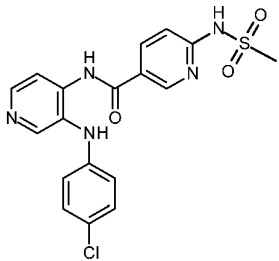
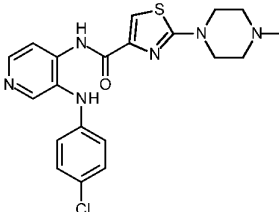
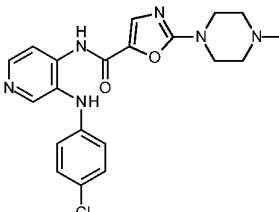


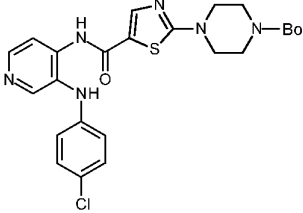
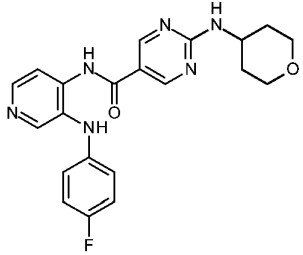
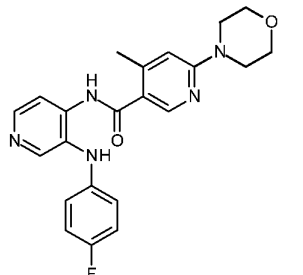
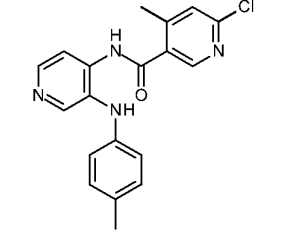
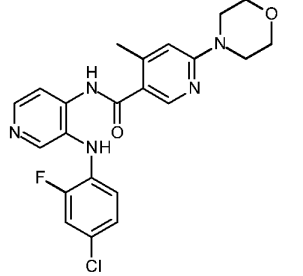
Int	Structure	Name	Intermediate(s), Form, Yield, LCMS, HPLC
67		N-{3-[(4-Chlorophenyl)amino]pyridin-4-yl}pyridine-4-carboxamide	From Intermediate 19 Yellow solid Yield 219mg, 58.3% LCMS (ES ⁺): 325.2 [MH] ⁺ HPLC: Rt 4.18min, 95.8% purity

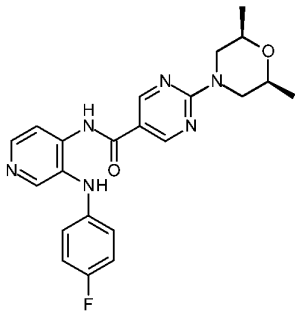
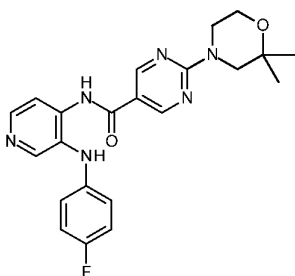
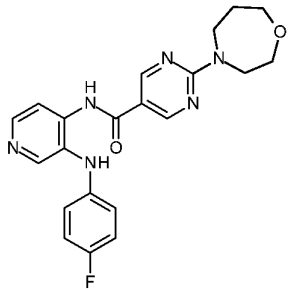
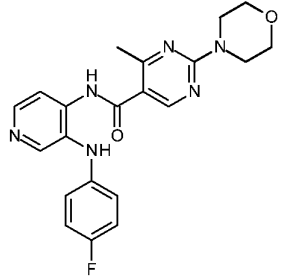
68		<i>N</i> -{3-[(4-Chlorophenyl)amino]pyridin-4-yl}-6-(morpholin-4-ylmethyl)pyridine-3-carboxamide	From Intermediates 19 and 61 Yellow solid Yield 282mg, 21.1% LCMS (ES ⁺): 424.1 [MH] ⁺
69		<i>N</i> -{3-[(4-Chlorophenyl)amino]pyridin-4-yl}-6-(morpholin-4-yl)pyridazine-3-carboxamide	From Intermediate 19 Yellow solid Yield 500mg, 58.2% LCMS (ES ⁺): 411.0 [MH] ⁺
70		<i>N</i> -{3-[(4-Chlorophenyl)amino]pyridin-4-yl}-5-(morpholin-4-yl)pyrazine-2-carboxamide	From Intermediates 19 and 62 Yellow oil Yield 633mg, 73.5% LCMS (ES ⁺): 411.0 [MH] ⁺
71		<i>N</i> -{3-[(4-Chlorophenyl)amino]pyridin-4-yl}-6-[(morpholin-4-yl)carbonyl]pyridine-3-carboxamide	From Intermediates 19 and 51 Yellow oil Yield 437mg, 54.9% LCMS (ES ⁺): 438.0 [MH] ⁺

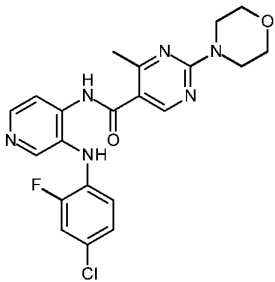
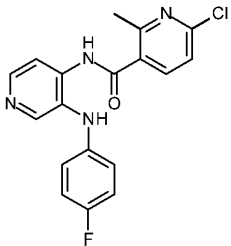
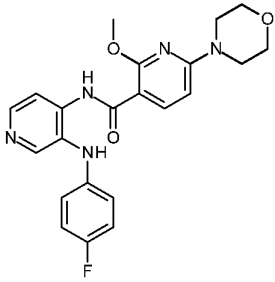
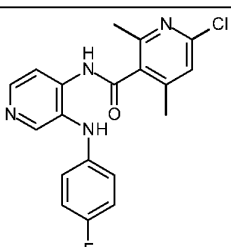
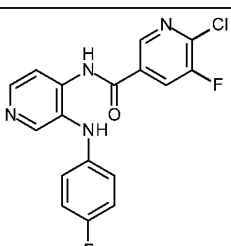
72		<i>N</i> -{3-[(4-chlorophenyl)amino]pyridin-4-yl}-5-[(oxan-4-yl)amino]pyrazine-2-carboxamide	From Intermediates 19 and 52 Yellow oil Yield 174mg, 45.6% LCMS (ES ⁺): 425.1 [MH] ⁺
73		<i>tert</i> -Butyl <i>N</i> -{1-[5-({3-[(4-chlorophenyl)amino]pyridin-4-yl}carbonyl)pyridin-2-yl]piperidin-4-yl}carbamate	From Intermediates 19 and 53 Off white solid Yield 954mg, 76.4% LCMS (ES ⁺): 523.1 [MH] ⁺ HPLC: Rt 5.16min, 97.8% purity
74		2-[(Cyclopropylmethyl)amino]- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediates 20 and 54 Yellow solid Yield 312mg, 32.3% LCMS (ES ⁺): 379.2 [MH] ⁺ HPLC: Rt 4.91min, 96.3% purity
75		2-(Cyclopropylamino)- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediates 20 and 55 Yellow solid Yield 659mg, 71.2% LCMS (ES ⁺): 365.1 [MH] ⁺ HPLC: Rt 4.41min, 68.3% purity

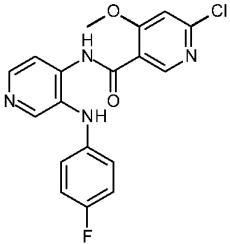
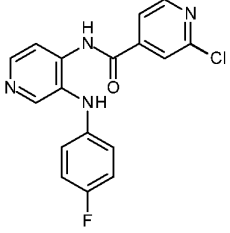
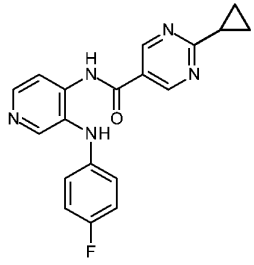
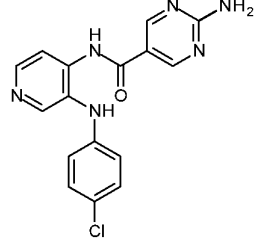
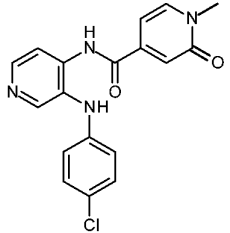
76		<i>N</i> -{3-[(4-Chlorophenyl)amino]pyridin-4-yl}-2-[(oxan-4-yl)amino]pyrimidine-5-carboxamide	From Intermediates 19 and 38 Yellow oil Yield 917mg, 86.3% LCMS (ES ⁺): 425.1 [MH] ⁺
77		<i>N</i> -{3-[(4-Fluorophenyl)amino]pyridin-4-yl}-2-(3-oxopiperazin-1-yl)pyrimidine-5-carboxamide	From Intermediates 20 and 39 Yellow gum Used crude (1.88g) LCMS (ES ⁺): 408.1 [MH] ⁺
78		<i>N</i> -{3-[(4-Chlorophenyl)amino]pyridin-4-yl}-2-(3-oxopiperazin-1-yl)pyrimidine-5-carboxamide	From Intermediates 19 and 39 Yellow solid Yield 712mg, 58.8% LCMS (ES ⁺): 424.1 [MH] ⁺
79		5- <i>N</i> -{3-[(4-Chlorophenyl)amino]pyridin-4-yl}-2- <i>N</i> -cyclopropylpyridine-2,5-dicarboxamide	From Intermediates 19 and 56 Yellow solid Yield 790mg, 84.9% LCMS (ES ⁺): 408.1 [MH] ⁺

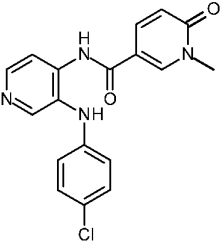
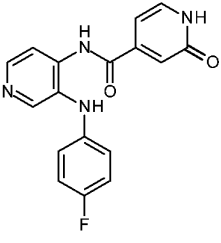
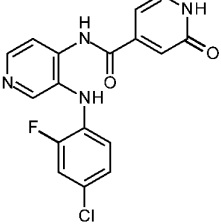
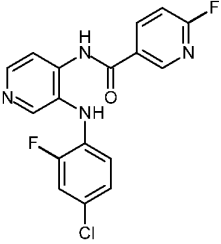
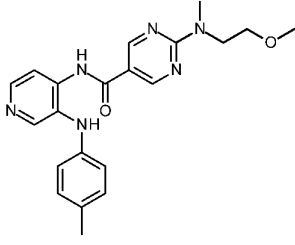
80		6-(3,6-Dihydro-2H-pyran-4-yl)- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}pyridazine-3-carboxamide	From Intermediates 20 and 63 Orange semi-solid Yield 467mg, 54.7% LCMS (ES ⁺): 392.2 [MH] ⁺ HPLC: Rt 4.87min, 50.9% purity
81		<i>N</i> -{3-[(4-chlorophenyl)amino]pyridin-4-yl}-6-methanesulfonamidopyridine-3-carboxamide	From Intermediates 19 and 57 Beige solid Yield 348mg, 40.6% LCMS (ES ⁺): 418.0 [MH] ⁺
82		<i>tert</i> -Butyl 4-[4-({3-[(4-chlorophenyl)amino]pyridin-4-yl}carbonyl)-1,3-thiazol-2-yl]piperazine-1-carboxylate	From Intermediates 19 and 58 White solid Yield 302mg, 66.8% LCMS (ES ⁺): 515.0 [MH] ⁺ HPLC: Rt 6.37min, 94.2% purity
83		<i>tert</i> -Butyl 4-[5-({3-[(4-chlorophenyl)amino]pyridin-4-yl}carbonyl)-1,3-oxazol-2-yl]piperazine-1-carboxylate	From Intermediates 19 and 59 Orange solid Used crude (602mg) LCMS (ES ⁺): 499.0 [MH] ⁺ HPLC: Rt 5.76min, 76.4% purity

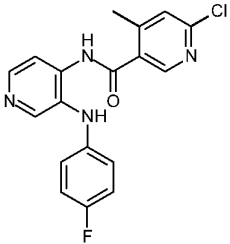
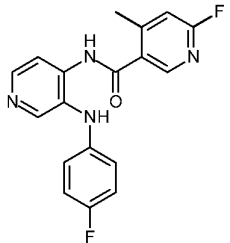
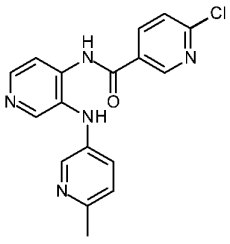
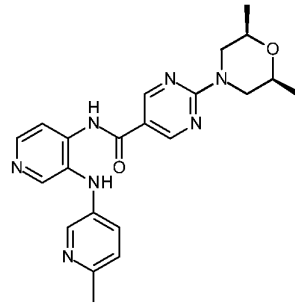
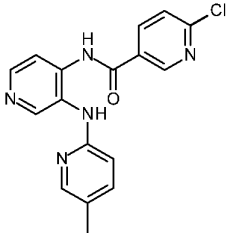
84		<i>tert</i> -Butyl 4-[5-({3-[(4-chlorophenyl)amino]pyridin-4-yl}carbamoyl)-1,3-thiazol-2-yl]piperazine-1-carboxylate	From Intermediates 19 and 60 Yellow solid Yield 417mg, 39.2% LCMS (ES ⁺): 515.1 [MH] ⁺ HPLC: Rt 5.95min, 39.1% purity
85		<i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}-2-[(oxan-4-yl)amino]pyrimidine-5-carboxamide	From Intermediates 20 and 38 Beige solid Yield 593mg, 59.0% LCMS (ES ⁺): 409.1 [MH] ⁺
86		<i>N</i> -{3-[(4-Fluorophenyl)amino]pyridin-4-yl}-4-methyl-6-(morpholin-4-yl)pyridine-3-carboxamide	From Intermediates 20 and 40 Light brown oil Yield 645mg, crude LCMS (ES ⁺): 408.2 [MH] ⁺
87		6-Chloro-4-methyl- <i>N</i> -{3-[(4-methylphenyl)amino]pyridin-4-yl}pyridine-3-carboxamide	From Intermediates 21 Dark oil used crude LCMS (ES ⁺): 353.0 [MH] ⁺
88		<i>N</i> -{3-[(4-Chloro-2-fluorophenyl)amino]pyridin-4-yl}-4-methyl-6-(morpholin-4-yl)pyridine-3-carboxamide	From Intermediates 22 and 40 Orange oil used crude LCMS (ES ⁺): 442.1 [MH] ⁺

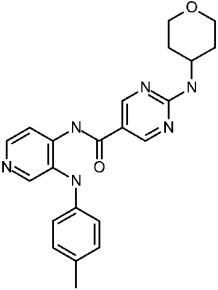
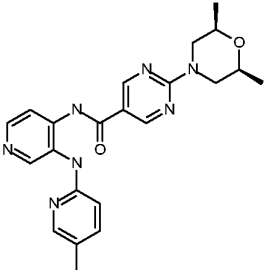
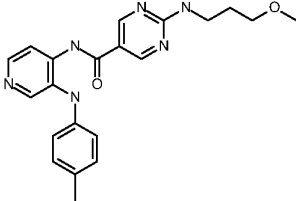
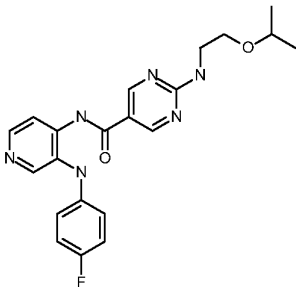
89		2-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediates 20 and 41 Yellow gum Yield 422mg, 79.0% LCMS (ES ⁺): 423.1 [MH] ⁺ HPLC: Rt 5.25min, 67.8% purity
90		2-(2,2-Dimethylmorpholin-4-yl)- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediates 20 and 42 Yellow gum Yield 338mg, 84.7% LCMS (ES ⁺): 423.1 [MH] ⁺ HPLC: Rt 5.12min, 75.5% purity
91		<i>N</i> -{3-[(4-Fluorophenyl)amino]pyridin-4-yl}-2-(1,4-oxazepan-4-yl)pyrimidine-5-carboxamide	From Intermediates 20 and 43 Yellow solid Yield 1.96g, 97.7% LCMS (ES ⁺): 409.2 [MH] ⁺
92		<i>N</i> -{3-[(4-Fluorophenyl)amino]pyridin-4-yl}-4-methyl-2-(morpholin-4-yl)pyrimidine-5-carboxamide	From Intermediates 20 and 44 Orange oil used crude LCMS (ES ⁺): 409.2 [MH] ⁺

93		<i>N</i> -{3-[(4-Chloro-2-fluorophenyl)amino]pyridin-4-yl}-4-methyl-2-(morpholin-4-yl)pyrimidine-5-carboxamide	From Intermediates 22 and 44 Orange oil used crude LCMS (ES ⁺): 443.1 [MH] ⁺
94		6-Chloro- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}-2-methylpyridine-3-carboxamide	From Intermediate 20 Orange oil used crude LCMS (ES ⁺): 357.1 [MH] ⁺
95		<i>N</i> -{3-[(4-Fluorophenyl)amino]pyridin-4-yl}-2-methoxy-6-(morpholin-4-yl)pyridine-3-carboxamide	From Intermediates 20 and 45 Yellow solid Yield 119mg, 44.3% LCMS (ES ⁺): 424.1 [MH] ⁺ HPLC: Rt 5.46min, 100% purity
96		6-Chloro- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}-2,4-dimethylpyridine-3-carboxamide	From Intermediate 20 used crude LCMS (ES ⁺): 371.0 [MH] ⁺
97		6-Chloro-5-fluoro- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}pyridine-3-carboxamide	From Intermediate 20 used crude LCMS (ES ⁺): 360.9 [MH] ⁺

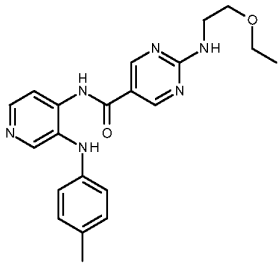
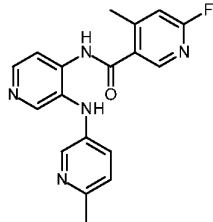
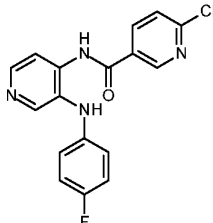
98		6-Chloro- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}-4-methoxypyridine-3-carboxamide	From Intermediate 20 used crude LCMS (ES ⁺): 373.0 [MH] ⁺
99		2-Chloro- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}pyridine-4-carboxamide	From Intermediate 20 Yellow solid Yield 608mg, 76.6% LCMS (ES ⁺): 343.1 [MH] ⁺
100		2-Cyclopropyl- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediate 20 Brown gum Yield 519mg, crude LCMS (ES ⁺): 349.8 [MH] ⁺
101		2-Amino- <i>N</i> -{3-[(4-chlorophenyl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediate 19 Orange oil used crude LCMS (ES ⁺): 340.7 [MH] ⁺
102		<i>N</i> -{3-[(4-Chlorophenyl)amino]pyridin-4-yl}-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxamide	From Intermediate 19 Orange oil used crude LCMS (ES ⁺): 355.1 [MH] ⁺

103		<i>N</i> -{3-[(4-Chlorophenyl)amino]pyridin-4-yl}-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide	From Intermediate 19 Orange oil used crude LCMS (ES ⁺): 355.1 [MH] ⁺
104		<i>N</i> -{3-[(4-Fluorophenyl)amino]pyridin-4-yl}-2-oxo-1,2-dihydropyridine-4-carboxamide	From Intermediate 20 Orange oil used crude LCMS (ES ⁺): 325.1 [MH] ⁺
105		<i>N</i> -{3-[(4-Chloro-2-fluorophenyl)amino]pyridin-4-yl}-2-oxo-1,2-dihydropyridine-4-carboxamide	From Intermediate 22 Orange oil used crude LCMS (ES ⁺): 359.1 [MH] ⁺
106		<i>N</i> -{3-[(4-Chloro-2-fluorophenyl)amino]pyridin-4-yl}-6-fluoropyridine-3-carboxamide	From Intermediate 22 Orange oil used crude LCMS (ES ⁺): 361.1 [MH] ⁺
107		2-[(2-Methoxyethyl)(methyl)amino]- <i>N</i> -{3-[(4-methylphenyl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediates 21 and 46 Dark oil used crude LCMS (ES ⁺): 393.0 [MH] ⁺

108		6-Chloro- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}-4-methylpyridine-3-carboxamide	From Intermediate 20 used crude LCMS (ES ⁺): 357.3 [MH] ⁺
109		6-Fluoro- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}-4-methylpyridine-3-carboxamide	From Intermediate 20 Pale yellow solid Yield 1.11g, 66.0% LCMS (ES ⁺): 341.0 [MH] ⁺
110		6-Chloro- <i>N</i> -{3-[(6-methylpyridin-3-yl)amino]pyridin-4-yl}pyridine-3-carboxamide	From Intermediate 23 Dark oil used crude LCMS (ES ⁺): 340.0 [MH] ⁺
111		2-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]- <i>N</i> -{3-[(6-methylpyridin-3-yl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediates 23 and 41 Dark orange oil used crude LCMS (ES ⁺): 420.1 [MH] ⁺
112		6-Chloro- <i>N</i> -{3-[(5-methylpyridin-2-yl)amino]pyridin-4-yl}pyridine-3-carboxamide	From Intermediate 24 Dark oil used crude LCMS (ES ⁺): 340.0 [MH] ⁺

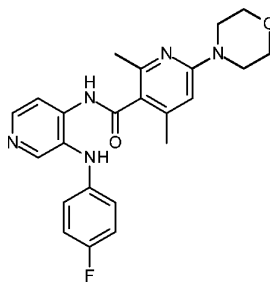
113		<i>N</i> -{3-[(4-Methylphenyl)amino]pyridin-4-yl}-2-[(oxan-4-yl)amino]pyrimidine-5-carboxamide	From Intermediates 21 and 38 Dark oil used crude LCMS (ES ⁺): 405.0 [MH] ⁺
114		2-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]- <i>N</i> -{3-[(5-methylpyridin-2-yl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediates 24 and 41 Orange oil used crude LCMS (ES ⁺): 420.0 [MH] ⁺
115		2-[(3-Methoxypropyl)amino]- <i>N</i> -{3-[(4-methylphenyl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediates 21 and 48 Dark oil used crude LCMS (ES ⁺): 393.1 [MH] ⁺
116		<i>N</i> -{3-[(4-Fluorophenyl)amino]pyridin-4-yl}-2-[[2-(propan-2-yloxy)ethyl]amino]pyrimidine-5-carboxamide	From Intermediates 20 and 49 Dark oil used crude LCMS (ES ⁺): 411.0 [MH] ⁺

117		<i>N</i> -{3-[(4-Methylphenyl)amino]pyridin-4-yl}-2-[[2-(propan-2-yloxy)ethyl]amino]pyrimidine-5-carboxamide	From Intermediates 21 and 49 Dark oil used crude LCMS (ES ⁺): 407.1 [MH] ⁺
118		<i>N</i> -{3-[(4-Fluorophenyl)amino]pyridin-4-yl}-2-(4-methyl-3-oxopiperazin-1-yl)pyrimidine-5-carboxamide	From Intermediates 20 and 50 Dark oil used crude LCMS (ES ⁺): 422.1 [MH] ⁺
119		<i>N</i> -{3-[(2,4-Difluorophenyl)amino]pyridin-4-yl}-6-(morpholin-4-yl)pyridine-3-carboxamide	From Intermediate 25 Orange oil used crude LCMS (ES ⁺): 412.0 [MH] ⁺
120		2-[(2-Ethoxyethyl)amino]- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediate 20 and 47 Orange oil used crude LCMS (ES ⁺): 397.1 [MH] ⁺

121		2-[(2-Ethoxyethyl)amino]- <i>N</i> -{3-[(4-methylphenyl)amino]pyridin-4-yl}pyrimidine-5-carboxamide	From Intermediate 21 and 47 Dark oil used crude LCMS (ES ⁺): 393.1 [MH] ⁺
122		6-Fluoro-4-methyl- <i>N</i> -{3-[(6-methylpyridin-3-yl)amino]pyridin-4-yl}pyridine-3-carboxamide	From Intermediate 23 Dark oil used crude LCMS (ES ⁺): 338.0 [MH] ⁺
123		6-Chloro- <i>N</i> -{3-[(4-fluorophenyl)amino]pyridin-4-yl}pyridine-3-carboxamide	From Intermediate 20 Yellow solid Yield 1.06g, 63.0% LCMS (ES ⁺): 342.9 [MH] ⁺ HPLC: Rt 4.86min, 91.2% purity

INTERMEDIATE 124

***N*-{3-[(4-Fluorophenyl)amino]pyridin-4-yl}-2,4-dimethyl-6-(morpholin-4-yl)pyridine-3-carboxamide**



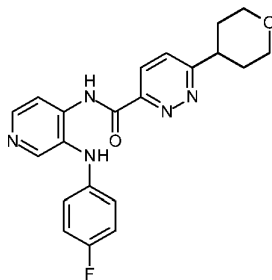
5

Intermediate 96 (crude) was dissolved in NMP (2mL) and morpholine (1.70mL, 19.7mmol) and Et₃N (708uL, 5.08mmol) were added. The reaction mixture was heated at 190°C in a microwave reactor for 30min and partitioned between EtOAc (50mL) and water (50mL). The organic fraction was washed with water (50mL),

brine (50mL), dried (MgSO₄), concentrated *in vacuo* and purified by column chromatography to give the title compound (783mg, 47.1%) as a yellow solid; LCMS (ES⁺): 422.0 [MH]⁺, HPLC: Rt: 3.99min, 83.2% purity.

5 INTERMEDIATE 125

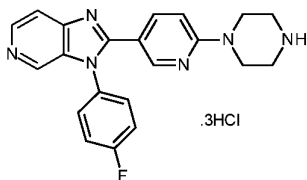
N-{3-[(4-Fluorophenyl)amino]pyridin-4-yl}-6-(oxan-4-yl)pyridazine-3-carboxamide



Intermediate 80 (220mg, 0.562mmol) was dissolved in MeOH (10mL), Pd/C (cat)
10 was added and the reaction mixture was stirred under hydrogen for 2h. The reaction mixture was filtered through Celite and concentrated *in vacuo* to give the crude title compound which was used without purification. LCMS (ES⁺): 394.2 [MH]⁺.

INTERMEDIATE 126

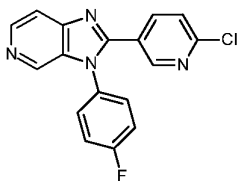
15 **1-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperazine trihydrochloride**



Intermediate 126 was prepared similarly to Example 50, using Intermediate 2
instead of Intermediate 1, to give the title compound (684mg, 100%) as a white
20 solid. LCMS (ES⁺): 375.1 [MH]⁺.

INTERMEDIATE 127

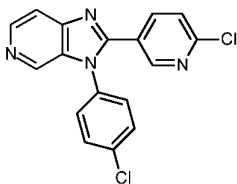
2-Chloro-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridine



Intermediate 2 (1.00g, 4.01mmol) and 2-chloro-5-pyridinecarboxaldehyde (682mg, 4.82mmol) were dissolved in EtOH (8mL) and Na₂S₂O₄ (2.79g, 16.1mmol) was added. The reaction mixture was heated in a microwave reactor at 160°C for 1h, diluted with water (25mL) and NaHCO₃ (25mL) and extracted into DCM (3x50mL). The combined organic fractions were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (375mg, 28.8%) as a yellow oil. LCMS (ES⁺): 325.1 [MH]⁺.

10 INTERMEDIATE 128

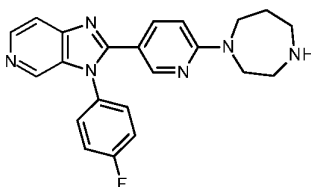
2-Chloro-5-[3-(4-chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridine



Intermediate 128 was prepared similarly to Intermediate 127, using Intermediate 1 instead of Intermediate 2, to give the title compound (81.0mg, 8.41%) as a yellow solid. LCMS (ES⁺): 341.1 [MH]⁺. HPLC: Rt: 5.10min, 97.0% purity.

INTERMEDIATE 129

1-[5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl]-1,4-diazepane



20

Intermediate 127 (375mg, 1.15mmol) and homopiperazine (578mg, 5.77mmol) were dissolved in DMA (6mL) and the reaction mixture was heated in a microwave reactor

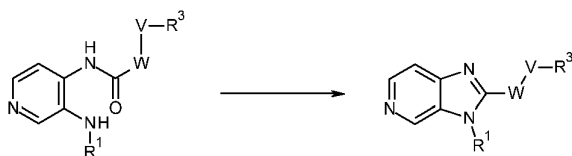
at 180°C for 30min and concentrated *in vacuo*. The residue was partitioned between DCM (50mL) and sat. aq. Na₂CO₃ (50mL) and the organic fraction dried (MgSO₄) and concentrated *in vacuo* to give the title compound (410mg, 91.5%) as a red oil. LCMS (ES⁺): 389.2 [MH]⁺.

5

INTERMEDIATES 130-133

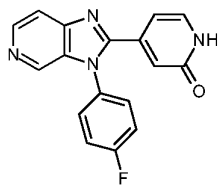
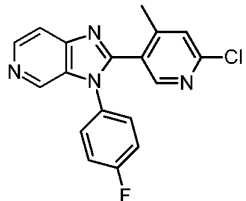
Intermediates 130-133 were prepared similarly to Example 1, by cyclisation of Intermediates 94, 99, 104 and 108; see Table 8 below.

Table 8: Cyclisation of Intermediates 94, 99, 104 and 108

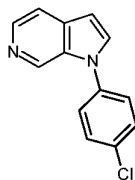


10

Ex	Structure	Name	Intermediate(s), Form, Yield, LCMS, HPLC
130		6-Chloro-3-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-methylpyridine	From Intermediate 94 Pale brown gum Yield 123mg, 29.5% LCMS (ES ⁺): 339.1 [MH] ⁺ HPLC: Rt 4.64min, 74.0% purity
131		2-Chloro-4-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridine	From Intermediate 99 Yellow solid Yield 397mg, 68.9% LCMS (ES ⁺): 325.1 [MH] ⁺ HPLC: Rt 4.48min, 80.2% purity

132		4-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,2-dihydropyridin-2-one	From Intermediate 104 Pale pink solid Yield 172mg, 22.7% LCMS (ES ⁺): 307.2 [MH] ⁺ HPLC: Rt 3.42min, 99.7% purity
133		2-Chloro-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyridine	From Intermediate 108 Yellow gum Yield 218mg, 63.1% LCMS (ES ⁺): 338.7 [MH] ⁺

INTERMEDIATE 134

1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridine

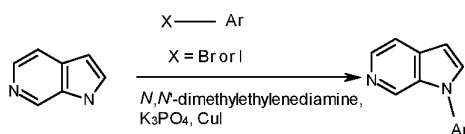
- 5 6-Azaindole (5.00g, 42.3mmol) was dissolved in DMF (150mL) under nitrogen and 1-chloro-4-iodo-benzene (12.1g, 50.8mmol), *N,N*-dimethylethylenediamine (911uL, 8.46mmol), K₃PO₄ (18.9g, 88.9mmol) and CuI (806mg, 4.23mmol) were added. The reaction mixture was heated at 150°C for 18h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was suspended in 1M aq.
- 10 Na₂CO₃ (250mL) and extracted into DCM (2x250mL). The combined organic fractions were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound as a yellow solid (8.58g, 88.6%). LCMS (ES⁺): 229.1 [MH]⁺. HPLC: Rt 4.48min, 98.6% purity.

15 INTERMEDIATE 135-138

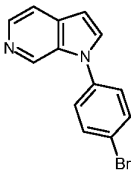
Intermediates 135-138 were prepared similarly to Intermediate 134, by arylation of 6-azaindole with the appropriate aryl or heteroaryl iodide or bromide; see Table 9 below.

Table 9: Arylations of 6-azaindole

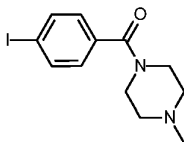
5



Ex	Structure	Name	Intermediate(s), Form, Yield, LCMS, HPLC
135		1-(4-Methylphenyl)-1H-pyrrolo[2,3-c]pyridine	Green gum Yield 800mg, 45.4% LCMS (ES ⁺): 209.1 [MH] ⁺ HPLC: Rt 4.65min, 99.7% purity.
136		1-Phenyl-1H-pyrrolo[2,3-c]pyridine	Green gum Yield 890mg, 54.0% LCMS (ES ⁺): 195.1 [MH] ⁺ HPLC: Rt 4.19min, 99.6% purity.
137		5-Methyl-2-{1H-pyrrolo[2,3-c]pyridin-1-yl}pyridine	Light yellow solid Yield 113mg, 6.38% LCMS (ES ⁺): 210.1 [MH] ⁺ HPLC: Rt 4.45min, 100% purity.

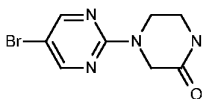
138		1-(4-Bromophenyl)-1H-pyrrolo[2,3-c]pyridine	Green solid Yield 1.14g, 24.7% LCMS (ES ⁺): 273.0 [MH] ⁺ HPLC: Rt 4.78min, 98.5% purity.
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INTERMEDIATE 139

1-[(4-Iodophenyl)carbonyl]-4-methylpiperazine

- 5 4-Iodobenzoic acid (500mg, 2.02mmol) and DMF (50uL) were dissolved in DCM (24mL), oxalyl chloride (182uL, 2.12mmol) was added drop-wise and the reaction mixture was stirred for 30min. DIPEA (421uL, 2.42mmol) and a solution of *N*-methylpiperazine (222mg, 2.22mmol) in DCM (1mL) were added and the reaction mixture was stirred for 30min, washed with sat. aq. NaHCO₃ (2x75mL), dried
- 10 (MgSO₄) and concentrated *in vacuo* to give the title compound (660mg, 99.2%) as a yellow solid. LCMS (ES⁺): 331.0 [MH]⁺. HPLC: Rt 4.05min, 99.6% purity.

INTERMEDIATE 140

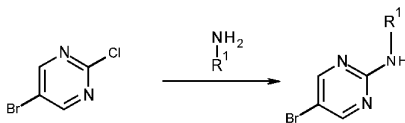
4-(5-Bromopyrimidin-2-yl)piperazin-2-one

- 15 5-Bromo-2-chloropyrimidine (750mg, 3.88mmol), DIPEA (878uL, 5.04mmol) and piperazin-2-one (427mg, 4.26mmol) were dissolved in MeCN (20mL). The reaction mixture was heated at 95°C for 1h then allowed to cool to RT overnight. The resulting solid was collected by filtration, washed with water (2x20mL) to give the
- 20 title compound (546mg, 54.8%) as a white solid. LCMS (ES⁺): 257.1 and 259.1 [MH]⁺. HPLC: Rt 4.68min, 98.6% purity.

INTERMEDIATE 141-142

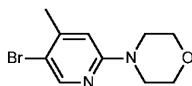
Intermediates 141-142 were prepared similarly to Intermediate 140, by coupling of 5-bromo-2-chloropyrimidine with the appropriate amine; see Table 10 below.

5 **Table 10: S_NAr with 5-bromo-2-chloropyrimidine**



Ex	Structure	Name	Intermediate(s), Form, Yield, LCMS, HPLC
141		5-Bromo- <i>N</i> -(oxan-4-yl)pyrimidin-2-amine	White solid Yield 645mg, 48.4% LCMS (ES ⁺): 258.0 [MH] ⁺
142		5-Bromo- <i>N</i> -(cyclopropylmethyl)pyrimidin-2-amine	Light yellow solid Yield 476mg, 80.7% LCMS (ES ⁺): 228.1 [MH] ⁺ HPLC: Rt 6.48min, 83.9% purity.

INTERMEDIATE 143

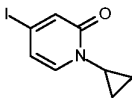
4-(5-Bromo-4-methylpyridin-2-yl)morpholine

10

5-Bromo-2-fluoro-4-methylpyridine (1.00g, 5.26mmol) and morpholine (1.38mL, 15.8mmol) were dissolved in MeCN (3.0mL) and the reaction mixture heated by microwave reactor at 140-160°C for 1.5h. The reaction mixture was diluted with EtOAc (40mL), washed with sat. aq. NaHCO₃ (40mL), dried (MgSO₄) and the solvents removed *in vacuo* to give the title compound (1.20g, 88.7%) as a white solid. LCMS (ES⁺): 257.0 [MH]⁺. HPLC: Rt 4.40min, 95.1% purity.

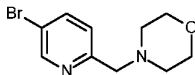
15

INTERMEDIATE 144

1-Cyclopropyl-4-iodo-1,2-dihydropyridin-2-one

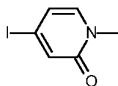
4-Iodo-1,2-dihydropyridin-2-one (1.00g, 4.52mmol), copper (II) acetate (879mg, 4.84mmol), 4,4-dipyridyl (756mg, 4.84mmol), cyclopropylboronic acid (875mg, 10.2mmol) and Na₂CO₃ (1.09g, 10.3mmol) in DCE (40mL) was stirred at 70°C for 18h. The reaction was quenched with sat. NH₄Cl (20mL) and water (50mL) and extracted with DCM (2x50mL), dried MgSO₄ and concentrated *in vacuo*. The crude material was purified by column chromatography to give the title compound (585mg, 49.5%) as a yellow oil. LCMS (ES⁺): 262.0 [MH]⁺.

INTERMEDIATE 145

4-[(5-Bromopyridin-2-yl)methyl]morpholine

5-Bromo-pyridine-2-carbaldehyde (1.00g, 5.38mmol) and morpholine (464uL, 5.38mmol) were dissolved in DCM (20mL) and NaBH(OAc)₃ (1.71g, 8.06mmol) was added. The reaction mixture was stirred at RT for 4d then heated at 50°C for 7h. Morpholine (464uL, 5.38mmol) and NaBH(OAc)₃ (1.71g, 8.06mmol) were added and the reaction was heated at 50°C for 16h. Water (50mL) and sat. aq. Na₂CO₃ sol. (50mL) were added and the aqueous fraction was then extracted with DCM (2x100mL) dried (MgSO₄), filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography to give the title compound (1.31g, 94.8%) as a yellow oil. LCMS (ES⁺): 257.0 [MH]⁺.

INTERMEDIATE 146

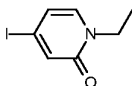
4-Iodo-1-methyl-1,2-dihydropyridin-2-one

4-Iodo-1,2-dihydropyridin-2-one (500mg, 2.26mmol), MeI (296uL, 4.75mmol) and

K₂CO₃ (688mg, 4.98mmol) were suspended in MeCN (20mL) and stirred for 18h. The reaction mixture was filtered and the solvents removed *in vacuo*. The residue was purified by column chromatography to give the title compound (411mg, 77.3%) as a white solid. LCMS (ES⁺): 236.0 [MH]⁺. HPLC: Rt 4.48min, 99.6% purity.

5

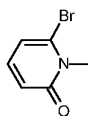
INTERMEDIATE 147

1-Ethyl-4-iodo-1,2-dihydropyridin-2-one

Intermediate 147 was prepared similarly to Intermediate 146, using ethyl iodide instead of methyl iodide, to give the title compound (347mg, 61.6%) as a yellow gum. LCMS (ES⁺): 250.0 [MH]⁺. HPLC: Rt 5.04min, 96.0% purity.

10

INTERMEDIATE 148

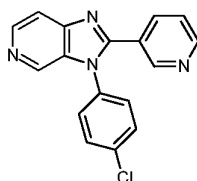
6-Bromo-1-methyl-1,2-dihydropyridin-2-one

15

Intermediate 148 was prepared similarly to Intermediate 146, using 2-bromo-6-hydroxypyridine instead of 4-iodo-1,2-dihydropyridin-2-one, to give the title compound (468mg, 86.6%) as an off white solid. LCMS (ES⁺): 188.1 and 190.1 [MH]⁺. HPLC: Rt 4.17min, 98.4% purity.

20

EXAMPLE 1

3-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridine

Intermediate 66 (297mg, 0.914mmol) was dissolved in AcOH (5mL) and heated using a microwave reactor at 100°C for 15min, diluted with water (50mL), basified

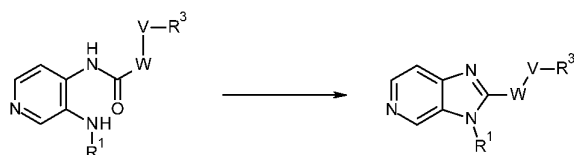
25

with Na₂CO₃ and extracted into DCM (3x50mL). The combined organic fractions were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound as a white solid (139mg, 49.5%). HRMS (ESI⁺) calcd for [MH]⁺ of C₁₇H₁₁ClN₄ 307.0750 found 307.0748. HPLC: Rt 4.22min, 99.8% purity.

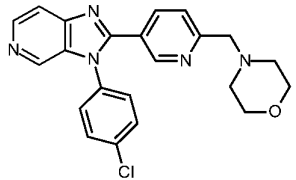
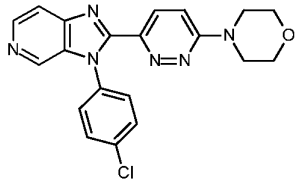
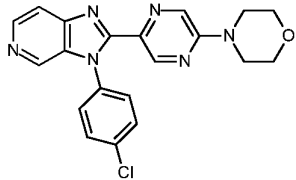
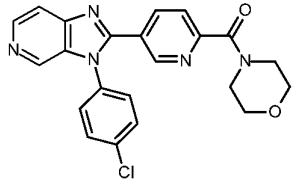
EXAMPLES 2-43

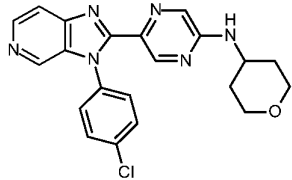
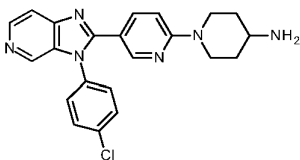
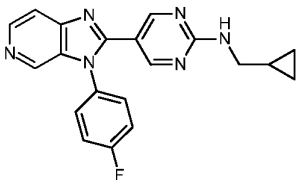
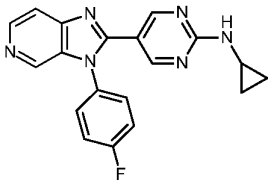
Examples 2-43 were prepared similarly to Example 1, by cyclisation of Intermediates 67-79, 81-86, 88-93, 95, 100-103, 105-106, 114-121, 124 and 125; see Table 11 below.

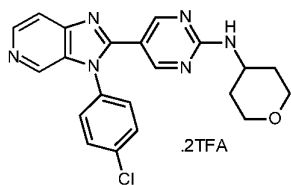
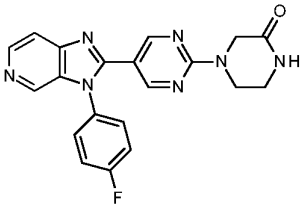
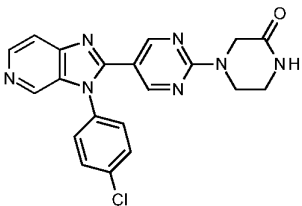
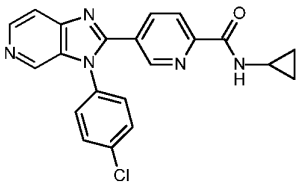
Table 11: Cyclisation of Intermediates 67-79, 81-86, 88-93, 95, 100-103, 105-106, 114-121, 124 and 125

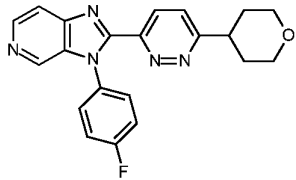
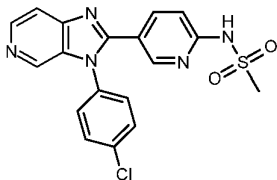
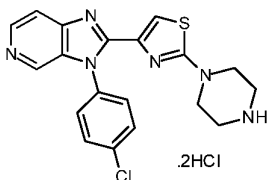
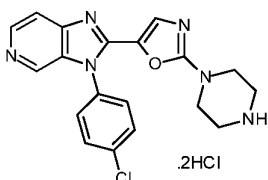


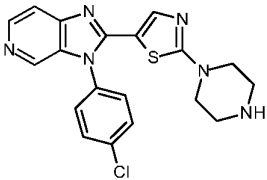
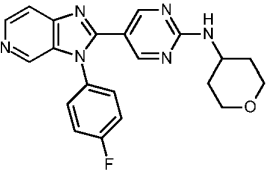
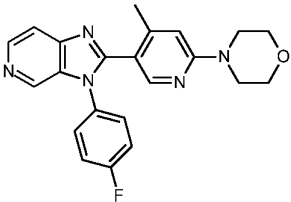
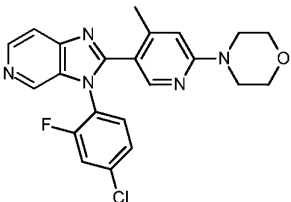
Ex	Structure	Name	Intermediate(s), Form, Yield, LCMS, HPLC
2		4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridine	From Intermediate 67 Light pink solid Yield 109mg, 52.7% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₇ H ₁₁ ClN ₄ 307.0750 found 307.0752. HPLC: Rt 3.90min, 99.8% purity

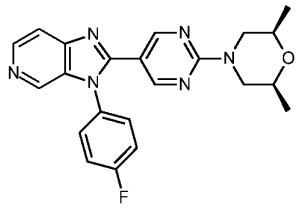
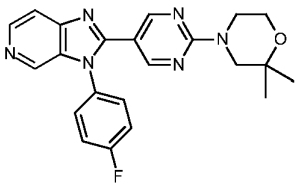
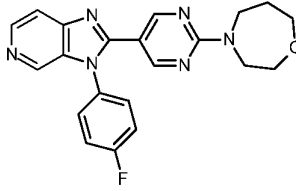
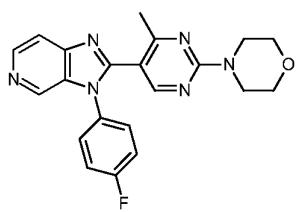
3		4-({5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]methyl)morpholine	From Intermediate 68 White solid Yield 105mg, 38.6% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₂₀ClN₅O 406.1435 found 406.1428. HPLC: Rt 3.65min, 100% purity
4		4-{6-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridazin-3-yl}morpholine	From Intermediate 69 White solid Yield 89.9mg, 18.8% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₀H₁₇ClN₆O 393.1230 found 393.1234. HPLC: Rt 4.71min, 98.4% purity
5		4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrazin-2-yl}morpholine	From Intermediate 70 White solid Yield 114mg, 18.9% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₀H₁₇ClN₆O 393.1230 found 393.1234. HPLC: Rt 4.79min, 100% purity
6		4-({5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}carbonyl)morpholine	From Intermediate 71 White solid Yield 170mg, 40.5% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₁₈ClN₅O₂ 420.1227 found 420.1228. HPLC: Rt 4.03min, 100% purity

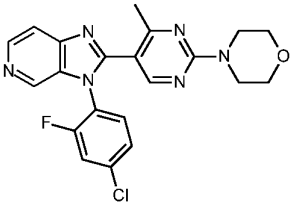
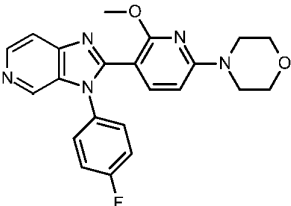
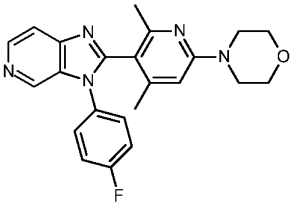
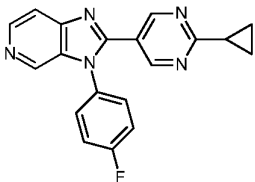
7		5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N-(oxan-4-yl)pyrazin-2-amine	From Intermediate 72 Yellow solid Yield 50.0mg, 30.0% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₉ ClN ₆ O 407.1387 found 407.1380. HPLC: Rt 4.86min, 100% purity
8		1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperidin-4-amine	From Intermediate 73 White solid Yield 24.2mg, 38.7% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₁ ClN ₆ 405.1594 found 405.1591. HPLC: Rt 3.52min, 100% purity
9		N-(Cyclopropylmethyl)-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine	From Intermediate 74 White solid Yield 24.6mg, 8.28% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₇ FN ₆ 361.1577 found 361.1594. HPLC: Rt 5.01min, 97.0% purity
10		N-Cyclopropyl-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine	From Intermediate 75 White solid Yield 30.9mg, 4.93% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₅ FN ₆ 347.1420 found 347.1422. HPLC: Rt 4.46min, 99.6% purity

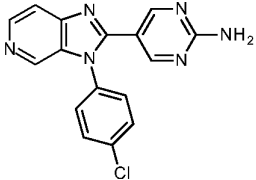
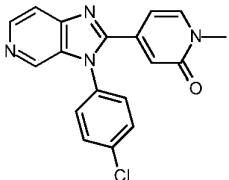
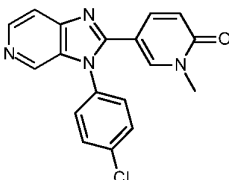
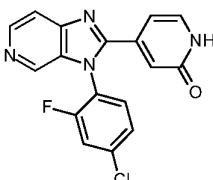
11		5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N-(oxan-4-yl)pyrimidin-2-amine; bis(trifluoroacetic acid)	From Intermediate 76 White solid Yield 73.8mg, 5.39% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₉ClN₆O 407.1387 found 407.1403. HPLC: Rt 4.76min, 100% purity
12		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}piperazin-2-one	From Intermediate 77 White solid Yield 104mg, 9.29% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₀H₁₆FN₇O 390.1479 found 390.1481. HPLC: Rt 4.01min, 100% purity
13		4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}piperazin-2-one	From Intermediate 78 White solid Yield 97.1mg, 14.2% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₀H₁₆ClN₇O 406.1183 found 406.1185. HPLC: Rt 4.25min, 99.5% purity
14		5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N-cyclopropylpyridine-2-carboxamide	From Intermediate 79 White solid Yield 100mg, 13.3% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₆ClN₅O 390.1122 found 390.1139. HPLC: Rt 4.81min, 100% purity

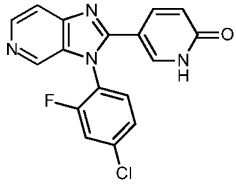
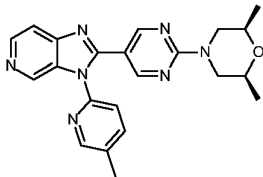
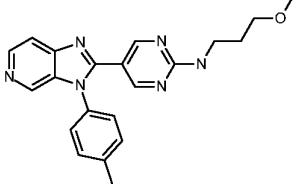
15		3-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-6-(oxan-4-yl)pyridazine	From Intermediate 125 Off white solid Yield 14.0mg, 6.63% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₈ FN ₅ O 376.1573 found 376.1575. HPLC: Rt 4.37min, 98.4% purity
16		<i>N</i> -{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}methanesulfonamide	From Intermediate 81 White solid Yield 163mg, 48.8% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₈ H ₁₄ ClN ₅ O ₂ S 400.0635 found 400.0631. HPLC: Rt 4.19min, 100% purity
17		1-{4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,3-thiazol-2-yl}piperazine dihydrochloride	From Intermediate 82 Yellow solid Yield 47.3mg, 17.3% * HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₇ ClN ₆ S 397.1002 found 397.1011. HPLC: Rt 3.44-3.55min, 100% purity
18		1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,3-oxazol-2-yl}piperazine dihydrochloride	From Intermediate 83 Orange solid Yield 58.0mg, 11.8% * HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₇ ClN ₆ O 381.1230 found 381.1241. HPLC: Rt 3.25min, 100% purity

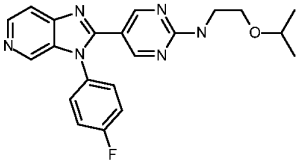
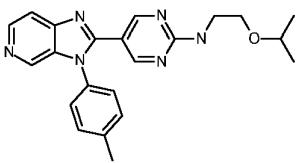
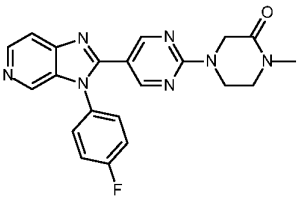
19		1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,3-thiazol-2-yl}piperazine	From Intermediate 84 Off white solid Yield 9.50mg, 2.96% * HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₇ ClN ₆ S 397.1002 found 397.1008. HPLC: Rt 3.41-3.53min, 99.3% purity
20		5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N-(oxan-4-yl)pyrimidin-2-amine	From Intermediate 85 White solid Yield 79.0mg, 13.9% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₉ FN ₆ O 391.1682 found 391.1693. HPLC: Rt 4.47min, 100% purity
21		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyridin-2-yl}morpholine	From Intermediate 86 White solid Yield 15.2mg, 2.17% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₀ FN ₅ O 390.1730 found 390.1721. HPLC: Rt 4.09min, 98.2% purity
22		4-{5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyridin-2-yl}morpholine	From Intermediate 88 Yellow solid Yield 16.0mg, 3.59% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₁₉ ClFN ₅ O 424.1340 found 424.134. HPLC: Rt 4.31min, 98.4% purity

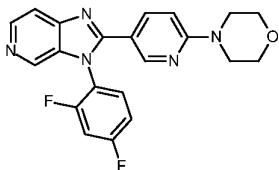
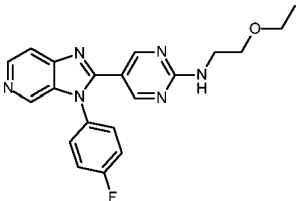
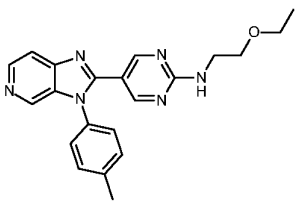
23		(2R,6S)-4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}-2,6-dimethylmorpholine	From Intermediate 89 Beige solid Yield 25.8mg, 6.39% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₁ FN ₆ O 405.1839 found 405.1843. HPLC: Rt 5.14min, 99.1% purity
24		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}-2,2-dimethylmorpholine	From Intermediate 90 White solid Yield 17.1mg, 5.28% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₁ FN ₆ O 405.1839 found 405.1852. HPLC: Rt 5.14min, 97.4% purity
25		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}-1,4-oxazepane	From Intermediate 91 White solid Yield 415mg, 43.5% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₉ FN ₆ O 391.1682 found 391.1682. HPLC: Rt 4.80min, 98.7% purity
26		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyrimidin-2-yl}morpholine	From Intermediate 92 White solid Yield 8.50mg, 1.76% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₉ FN ₆ O 391.1682 found 391.1676. HPLC: Rt 4.54min, 97.8% purity

27		4-{5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyrimidin-2-yl}morpholine	From Intermediate 93 White solid Yield 37.0mg, 8.28% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₈ ClFN ₆ O 425.1293 found 425.1296. HPLC: Rt 4.92min, 99.8% purity
28		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-6-methoxypyridin-2-yl}morpholine	From Intermediate 95 Pale yellow solid Yield 47.4mg, 41.6% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₀ FN ₅ O ₂ 406.1679 found 406.1683. HPLC: Rt 5.02min, 99.5% purity
29		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4,6-dimethylpyridin-2-yl}morpholine	From Intermediate 124 Off white solid Yield 15.0mg, 2.00% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₃ H ₂₂ FN ₅ O 404.1887 found 404.1889. HPLC: Rt 3.74min, 99.5% purity
30		2-Cyclopropyl-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidine	From Intermediate 100 Off white solid Yield 50.2mg, 17.3% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₄ FN ₅ 332.1311 found 332.1313. HPLC: Rt 4.59min, 99.7% purity

31		5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine	From Intermediate 101 Off white solid Yield 14.0mg, 3.16% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₆ H ₁₁ ClN ₆ 323.0812 found 323.0815. HPLC: Rt 3.79min, 100% purity
32		4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1-methyl-1,2-dihydropyridin-2-one	From Intermediate 102 White solid Yield 109mg, 17.7% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₈ H ₁₃ ClN ₄ O 337.0856 found 337.0859. HPLC: Rt 4.07min, 98.8% purity
33		5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1-methyl-1,2-dihydropyridin-2-one	From Intermediate 103 Off white solid Yield 24.0mg, 7.83% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₈ H ₁₃ ClN ₄ O 337.0856 found 337.0857. HPLC: Rt 4.14min, 99.6% purity
34		4-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,2-dihydropyridin-2-one	From Intermediate 105 White solid Yield 15.0mg, 1.05% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₇ H ₁₀ ClFN ₄ O 341.0605 found 341.0607. HPLC: Rt 3.55min, 100% purity

35		5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,2-dihydropyridin-2-one	From Intermediate 106 White solid Yield 41.0mg, 5.72% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₇H₁₀ClFN₄O 341.0605 found 341.0613. HPLC: Rt 3.65min, 100% purity
36		(2R,6S)-2,6-Dimethyl-4-{5-[3-(5-methylpyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 114 White solid Yield 26.0mg, 3.71% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₂₃N₇O 402.2042 found 402.2047. HPLC: Rt 4.96min, 98.8% purity
37		N-(3-Methoxypropyl)-5-[3-(4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine	From Intermediate 115 White solid Yield 65.0mg, 8.65% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₂₂N₆O 375.1933 found 375.1935. HPLC: Rt 4.66min, 99.3% purity

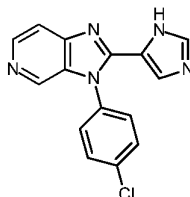
38		5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N-[2-(propan-2-yloxy)ethyl]pyrimidin-2-amine	From Intermediate 116 White solid Yield 181mg, 23.4% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₂₁FN₆O 393.1839 found 393.1823. HPLC: Rt 4.80 min, 99.4% purity
39		5-[3-(4-Methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N-[2-(propan-2-yloxy)ethyl]pyrimidin-2-amine	From Intermediate 117 White solid Yield 55.7mg, 7.14% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₂₄N₆O 389.2090 found 389.2083. HPLC: Rt 5.01min, 100% purity
40		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}-1-methylpiperazin-2-one	From Intermediate 118 White solid Yield 128mg, 21.5% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₈FN₇O 404.1635 found 404.1620. HPLC: Rt 4.22min, 100% purity

41		4-{5-[3-(2,4-Difluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 119 White solid Yield 41.1mg, 6.60% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₇ F ₂ N ₅ O 394.1479 found 394.1469. HPLC: Rt 4.47min, 99.2% purity
42		<i>N</i> -(2-Ethoxyethyl)-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine	From Intermediate 120 Off white solid Yield 154mg, 27.6% LCMS (ES ⁺): 379.0 [MH] ⁺ HPLC: Rt 4.70min, 99.1% purity
43		<i>N</i> -(2-Ethoxyethyl)-5-[3-(4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine	From Intermediate 121 White solid Yield 119mg, 21.1% LCMS (ES ⁺): 375.1 [MH] ⁺ HPLC: Rt 4.94min, 99.1% purity

* Boc deprotection under reaction conditions

EXAMPLE 44

5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1H-imidazole



5

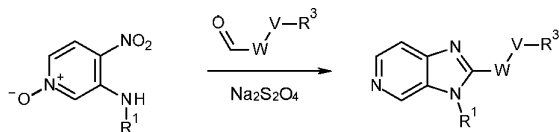
Intermediate 1 (200mg, 0.753mmol) and imidazole-4-carboxaldehyde (86.8mg, 0.903mmol) were dissolved in EtOH (5mL) and Na₂S₂O₄ (524mg, 3.01mmol) was

added. The reaction mixture was heated using a microwave reactor at 160°C for 1h, diluted with sat. aq. NaHCO₃ (25mL) and water (25mL), and extracted into DCM (3x50mL). The combined organic fractions were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound as a yellow solid (51.2mg, 23.0%). HRMS (ESI⁺) calcd for [MH]⁺ of C₁₅H₁₀ClN₅ 296.0703 found 296.0709. HPLC: Rt 3.24min, 100% purity.

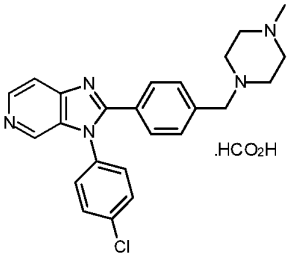
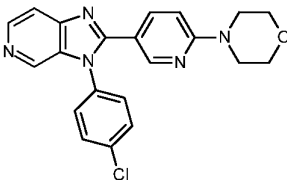
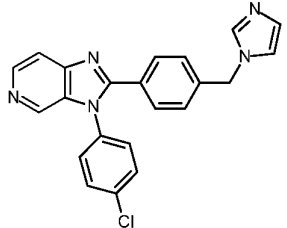
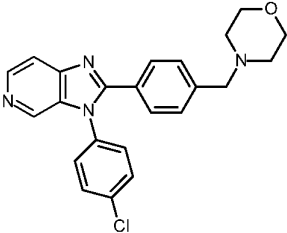
EXAMPLES 45-72

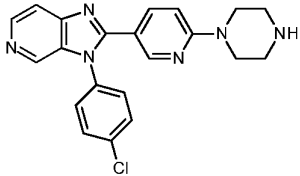
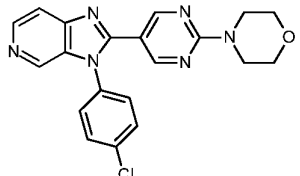
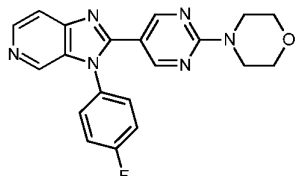
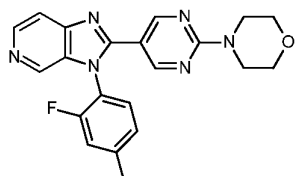
Examples 45-72 were prepared similarly to Example 44, by reductive condensation of Intermediates 1-11 with the appropriate aldehyde; see Table 12 below.

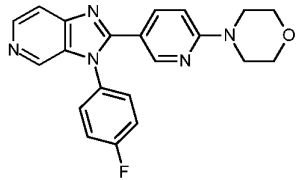
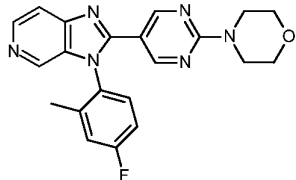
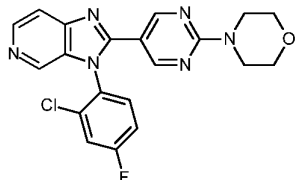
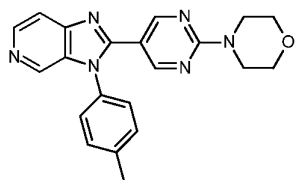
Table 12: Reductive condensations of Intermediates 1-11

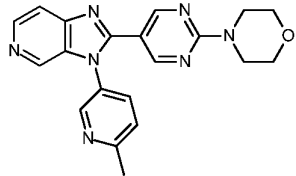
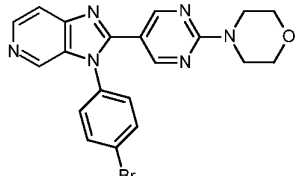
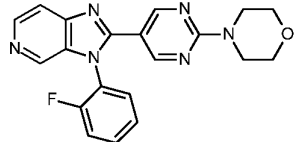
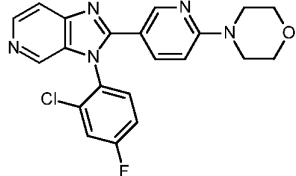


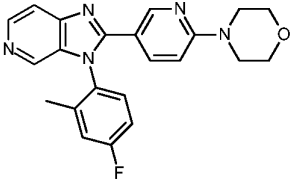
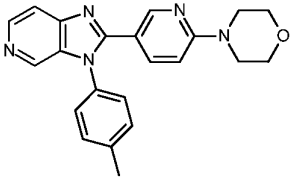
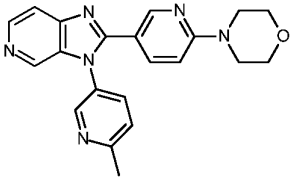
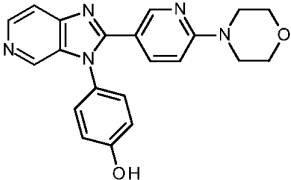
Ex	Structure	Name	Intermediate(s) used, Form, Yield, LCMS, HPLC
45		1-({3-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]phenyl)methyl)-4-methylpiperazine; formic acid	From Intermediate 1 White solid Yield 34.6mg, 9.91% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₄ H ₂₄ ClN ₅ 418.1798 found 418.1794. HPLC: Rt 3.51min, 99.0% purity

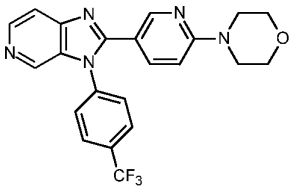
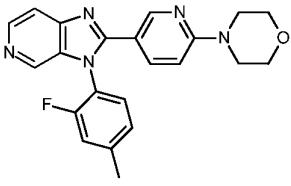
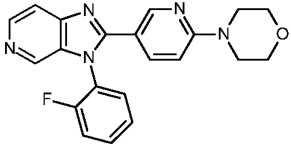
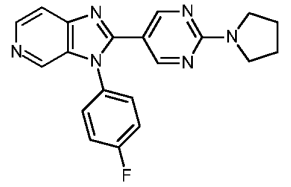
46		1-({4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]phenyl)methyl)-4-methylpiperazine; formic acid	From Intermediate 1 Light yellow solid Yield 42.0mg, 12.0% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₄ H ₂₄ ClN ₅ 418.1798 found 418.1813. HPLC: Rt 3.43min, 99.1% purity
47		4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 1 White solid Yield 70.9mg, 20.9% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₈ ClN ₅ O 392.1278 found 392.1282. HPLC: Rt 4.49min, 100% purity
48		1-({4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]phenyl)methyl)-1H-imidazole	From Intermediate 1 Orange gum Yield 39.4mg, 11.4% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₁₆ ClN ₅ 386.1172 found 386.1174. HPLC: Rt 3.90min, 100% purity
49		4-({4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]phenyl)methyl)morpholine	From Intermediate 1 Yellow solid Yield 9.81mg, 2.84% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₃ H ₂₁ ClN ₄ O 405.1482 found 405.1478. HPLC: Rt 3.85min, 100% purity

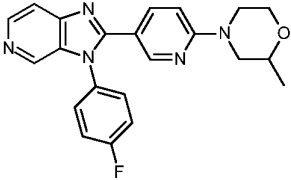
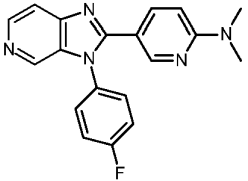
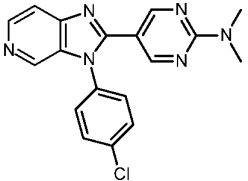
50		1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperazine	From Intermediate 1 Yellow solid Yield 3.10mg, 1.39% * HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₉ ClN ₆ 391.1438 found 391.1427. HPLC: Rt 3.51min, 100% purity
51		4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 1 White solid 2.75mg, 0.73% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₇ ClN ₆ O 393.1230 found 393.1234. HPLC: Rt 5.06min, 97.9% purity
52		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 2 White solid Yield 166mg, 36.6% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₇ FN ₆ O 377.1526 found 377.1514. HPLC: Rt 4.68min, 98.1% purity
53		4-{5-[3-(2-Fluoro-4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 3 White solid Yield 40.1mg, 13.5% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₉ FN ₆ O 391.1682 found 391.1674. HPLC: Rt 4.77min, 99.3% purity

54		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 2 White solid Yield 42.1mg, 14.0% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₈ FN ₅ O 376.1573 found 376.1560. HPLC: Rt 4.20min, 98.2% purity
55		4-{5-[3-(4-Fluoro-2-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 4 Pale yellow solid Yield 22.2mg, 3.74% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₉ FN ₆ O 391.1682 found 391.1679. HPLC: Rt 4.67min, 98.2% purity
56		4-{5-[3-(2-Chloro-4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 5 Off white solid Yield 32.4mg, 4.97% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₆ ClFN ₆ O 411.1136 found 411.1127. HPLC: Rt 4.72min, 100% purity
57		4-{5-[3-(4-Methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 6 White solid Yield 35.7mg, 5.22% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₂₀ N ₆ O 373.1777 found 373.1763. HPLC: Rt 4.80min, 99.4% purity

58		4-{5-[3-(6-Methylpyridin-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 7 Off white solid Yield 39.0mg, 5.14% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₉ N ₇ O 374.1729 found 374.1736. HPLC: Rt 3.90min, 99.1% purity
59		4-{5-[3-(4-Bromophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 8 White solid Yield 55.0mg, 7.80% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₇ BrN ₆ O 437.0725 found 437.0717. HPLC: Rt 5.15min, 99.0% purity
60		4-{5-[3-(2-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 9 White solid Yield 18.0mg, 2.38% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₇ FN ₆ O 377.1526 found 377.1515. HPLC: Rt 4.54min, 99.4% purity
61		4-{5-[3-(2-Chloro-4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 5 Pale yellow solid Yield 23.0mg, 3.54% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₇ ClFN ₅ O 410.1184 found 410.1189. HPLC: Rt 4.54min, 99.2% purity

62		4-{5-[3-(4-Fluoro-2-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 4 Pale yellow solid Yield 21.1mg, 3.57% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₂₀FN₅O 390.1730 found 390.1723. HPLC: Rt 4.50min, 99.3% purity
63		4-{5-[3-(4-Methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 6 White solid Yield 72.0mg, 9.51% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₂₁N₅O 372.1824 found 372.1820. HPLC: Rt 4.75min, 100% purity
64		4-{5-[3-(6-Methylpyridin-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 7 White solid Yield 52.0mg, 7.24% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₂₀N₆O 373.1777 found 373.1768. HPLC: Rt 3.69min, 100% purity
65		4-{2-[6-(Morpholin-4-yl)pyridin-3-yl]-3H-imidazo[4,5-c]pyridin-3-yl}phenol	From Intermediate 10 Off white solid Yield 106mg, 14.0% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₉N₅O₂ 374.1617 found 374.1618. HPLC: Rt 3.88min, 99.5% purity

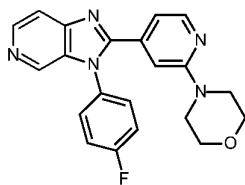
66		4-(5-{3-[4-(Trifluoromethyl)phenyl]-3H-imidazo[4,5-c]pyridin-2-yl}pyridin-2-yl)morpholine	From Intermediate 11 Off white solid Yield 22.0mg, 3.09% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₁₈ F ₃ N ₅ O 426.1541 found 426.1549. HPLC: Rt 4.88min, 99.5% purity
67		4-{5-[3-(2-Fluoro-4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 3 Pale yellow solid Yield 78.3mg, 10.6% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₀ FN ₅ O 390.1730 found 390.1729. HPLC: Rt 4.66min, 99.7% purity
68		4-{5-[3-(2-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 9 White solid Yield 73.0mg, 9.69% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₈ FN ₅ O 376.1573 found 376.1584. HPLC: Rt 4.33min, 99.5% purity
69		5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-(pyrrolidin-1-yl)pyrimidine	From Intermediate 2 White solid Yield 42.2mg, 7.29% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₇ FN ₆ 361.1577 found 361.1584. HPLC: Rt 4.83min, 98.5% purity

70		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}-2-methylmorpholine	From Intermediates 2 and 65 Orange solid Yield 42.7mg, 9.11% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₀ FN ₅ O 390.1730 found 390.1726. HPLC: Rt 4.54min, 99.4% purity
71		5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N,N-dimethylpyridin-2-amine	From Intermediate 2 White solid Yield 84.0mg, 12.6% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₆ FN ₅ 334.1468 found 334.1475. HPLC: Rt 3.72min, 100% purity
72		5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N,N-dimethylpyrimidin-2-amine	From Intermediates 1 and 64 White solid Yield 12.6mg, 1.91% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₈ H ₁₅ ClN ₆ 351.1125 found 351.1125. HPLC: Rt 4.90min, 100% purity

* Additional Boc deprotection step incorporated

EXAMPLE 73

4-{4-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine

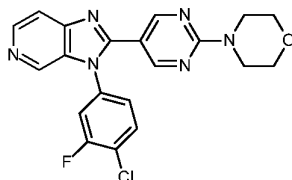


Intermediate 20 (250mg, 1.24mmol), 2-(morpholin-4-yl)pyridine-4-carbaldehyde (238mg, 1.24mmol) and $\text{Na}_2\text{S}_2\text{O}_4$ (646mg, 3.71mmol) were suspended in EtOH (2mL) and the reaction mixture was heated at 150°C in a microwave reactor for 45min. The reaction mixture was poured into 1M aq. Na_2CO_3 (25mL) and extracted with DCM (2x25mL). The combined organic fractions were dried (MgSO_4) and concentrated *in vacuo*. The residue was triturated from MeOH (2mL) to give the title compound (101mg, 21.7%) as an off white solid. HRMS (ESI^+) calcd for $[\text{MH}]^+$ of $\text{C}_{21}\text{H}_{18}\text{FN}_5\text{O}$ 376.1573 found 376.1573. HPLC: Rt 3.89min, 97.8% purity.

10

EXAMPLE 74

4-{5-[3-(4-Chloro-3-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine

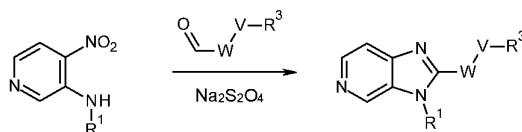


Intermediate 13 (200mg, 0.747mmol), 2-(morpholin-4-yl)pyrimidine-5-carbaldehyde (188mg, 0.971mmol) and $\text{Na}_2\text{S}_2\text{O}_4$ (520mg, 2.99mmol) were suspended in EtOH (5mL) and the reaction mixture was heated using a microwave reactor at 160°C for 1h. The reaction mixture was diluted with 1M aq. Na_2CO_3 (40mL) and extracted into DCM (2x50mL). The combined organic fractions were dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography and by reverse phase HPLC to give the title compound (36.6mg, 11.9%) as an off white solid. HRMS (ESI^+) calcd for $[\text{MH}]^+$ of $\text{C}_{20}\text{H}_{16}\text{ClFN}_6\text{O}$ 411.1136 found 411.1133. HPLC: Rt 5.09min, 99.7% purity.

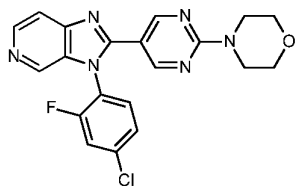
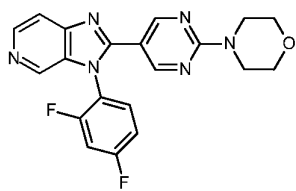
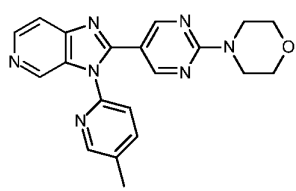
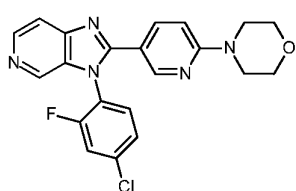
25 EXAMPLES 75-84

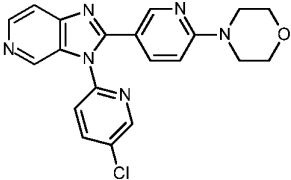
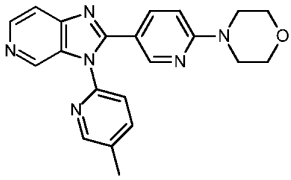
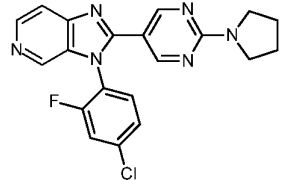
Examples 75-84 were prepared similarly to Example 74, by reductive condensation of Intermediates 14-18 with the appropriate aldehyde; see Table 13 below.

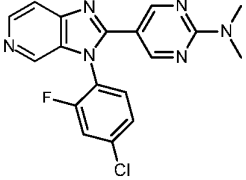
Table 13: Reductive condensations of Intermediates 14-18



Ex	Structure	Name	Intermediate(s) used, Form, Yield, LCMS, HPLC
75		4-{5-[3-(5-Chloropyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine; tris(trifluoroacetic acid)	From Intermediate 14 White solid Yield 29.0mg, 4.47% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₆ ClN ₇ O 394.1183 found 394.1168. HPLC: Rt 4.68min, 97.8% purity
76		4-{5-[3-(5-Fluoropyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 15 White solid Yield 53.2mg, 7.49% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₆ FN ₇ O 378.1479 found 378.1473. HPLC: Rt 4.36min, 98.4% purity

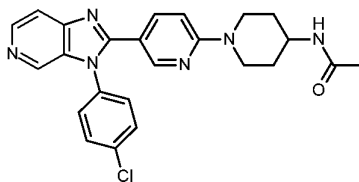
77		4-{5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 16 Yellow solid Yield 186mg, 15.4% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₆ ClFN ₆ O 411.1136 found 411.1142. HPLC: Rt 5.09min, 97.6% purity
78		4-{5-[3-(2,4-Difluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 17 Pale yellow solid Yield 39.2mg, 4.54% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₆ F ₂ N ₆ O 395.1432 found 395.1436. HPLC: Rt 4.76min, 99.6% purity
79		4-{5-[3-(5-Methylpyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 18 Off white solid Yield 46.1mg, 9.47% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₉ N ₇ O 374.1729 found 374.1736. HPLC: Rt 4.30min, 99.6% purity
80		4-{5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 16 White solid Yield 41.0mg, 12.8% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₇ ClFN ₅ O 410.1184 found 410.1187. HPLC: Rt 4.58min, 99.6% purity

81		4-{5-[3-(5-Chloropyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 14 White solid Yield 7.05mg, 2.57% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₀H₁₇ClN₆O 393.1230 found 393.1226. HPLC: Rt 4.45min, 97.9% purity
82		4-{5-[3-(5-Methylpyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 18 White solid Yield 38.0mg, 7.83% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₂₀N₆O 373.1777 found 373.1787. HPLC: Rt 4.03min, 99.4% purity
83		5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-(pyrrolidin-1-yl)pyrimidine	From Intermediate 16 White solid Yield 8.20mg, 2.22% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₀H₁₆ClFN₆ 395.1187 found 395.1190. HPLC: Rt 5.09min, 100% purity

84		5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N,N-dimethylpyrimidin-2-amine	From Intermediates 16 and 64 Light yellow solid Yield 63.7mg, 13.6% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₈H₁₄ClFN₆ 369.1031 found 369.1031. HPLC: Rt 4.93min, 100% purity
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EXAMPLE 85

N-(1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperidin-4-yl)acetamide

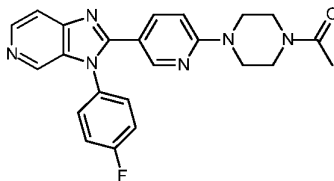


5

Example 8 (100mg, 0.247mmol), Et₃N (41.2uL, 0.296mmol) and acetyl chloride (19.3uL, 0.272mmol) were dissolved in DCM (10mL) and the reaction mixture was stirred for 2h and concentrated *in vacuo*. The residue was purified by column chromatography and partitioned between DCM (20mL) and sat. aq. NaHCO₃ (20mL). The organic fraction was washed with sat. aq. NaHCO₃ (20mL), dried (MgSO₄) and concentrated *in vacuo* to give the title compound (61.6mg, 55.8%) as a light yellow solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₄H₂₃ClN₆O 447.1700 found 447.1701. HPLC: Rt 3.98min, 99.7% purity.

15 EXAMPLE 86

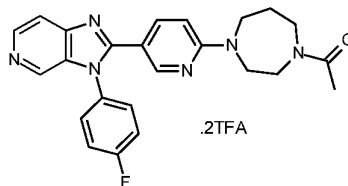
1-(4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperazin-1-yl)ethan-1-one



Example 86 was prepared similarly to Example 85, using Intermediate 126 instead of Example 8, to give the title compound (227mg, 38.7%) as a white solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₃H₂₁FN₆O 417.1839 found 417.1851. HPLC: Rt 4.26min,
 5 100% purity.

EXAMPLE 87

1-(4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}-1,4-diazepan-1-yl)ethan-1-one; bis(trifluoroacetic acid)

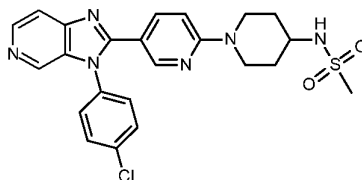


Example 87 was prepared similarly to Example 85, using Intermediate 129 instead of Example 8, to give the title compound (143mg, 41.2%) as a pink gum. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₄H₂₃FN₆O 431.1996 found 431.1997. HPLC: Rt 4.41min,
 10 99.7% purity.

15

EXAMPLE 88

N-(1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperidin-4-yl)methanesulfonamide

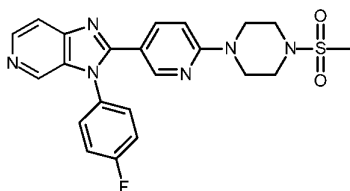


Example 8 (100mg, 0.247mmol), Et₃N (41.2uL, 0.296mmol) and methanesulfonyl chloride (26.8uL, 0.346mmol) were dissolved in DCM (10mL) and the reaction mixture was stirred for 2h, diluted with DCM (20mL), washed with sat. aq. NaHCO₃

(30mL), dried (MgSO₄) and concentrated *in vacuo*. The residue was triturated from MeOH (3mL) and collected by filtration to give the title compound (30.6mg, 25.7%) as a yellow solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₃H₂₃ClN₆O₂S 483.1370 found 483.1375. HPLC: Rt 4.18min, 99.4% purity.

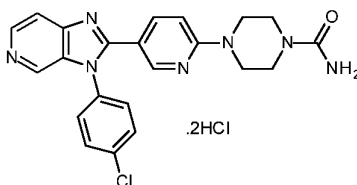
5

EXAMPLE 89

1-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}-4-methanesulfonylpiperazine

- 10 Example 89 was prepared similarly to Example 88, using Intermediate 126 instead of Example 8, to give the title compound (44.5mg, 10.3%) as a yellow solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₂₁FN₆O₂S 453.1509 found 453.1522. HPLC: Rt 4.59min, 98.2% purity.

15 EXAMPLE 90

4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperazine-1-carboxamide dihydrochloride

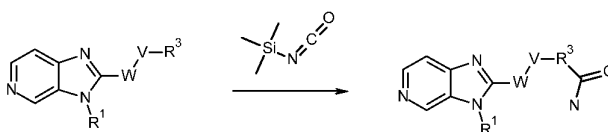
- Example 50 trihydrochloride (94.5mg, 0.189mmol) was dissolved in DCM (5mL),
20 and DIPEA (145uL, 0.831mmol) and trimethylsilyl isocyanate (30.7uL, 0.227mmol) were added. The reaction mixture was stirred for 16h, diluted with 1M aq. Na₂CO₃ (25mL) and extracted into DCM (3x25mL). The combined organic fractions were dried (MgSO₄) and concentrated *in vacuo*. The residue was dissolved in 1.25M HCl in EtOH (5mL), stirred for 1h and concentrated *in vacuo*. The residue was purified by
25 reverse phase HPLC to give the title compound (21.4mg, 22.3%) as a yellow solid.

HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₂₀ClN₇O 434.1496 found 434.1497. HPLC: Rt 4.19min, 98.5% purity.

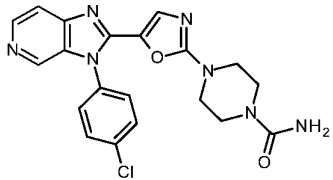
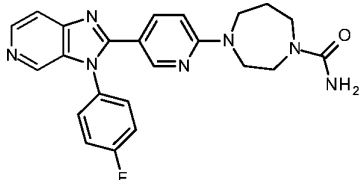
EXAMPLES 91-94

- 5 Examples 91-94 were prepared similarly to Example 90, by reaction of Examples 8, 18 and Intermediates 126, 129 with trimethylsilyl isocyanate; see Table 14 below.

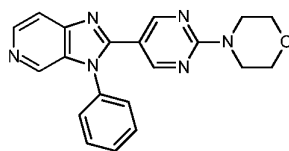
Table 14: Reaction of Examples 8, 18 and Intermediates 126, 129 with trimethylsilyl isocyanate



Ex	Structure	Name	Intermediate(s) used, Form, Yield, LCMS, HPLC
91		(1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperidin-4-yl)urea; bis(trifluoroacetic acid)	From Example 8 Yellow solid Yield 36.3mg, 21.7% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₃ H ₂₂ ClN ₇ O 448.1653 found 448.1656. HPLC: Rt 3.75min, 98.7% purity
92		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperazine-1-carboxamide	From Intermediate 126 White solid Yield 44.0mg, 11.1% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₀ FN ₇ O 418.1791 found 418.1795. HPLC: Rt 3.88min, 100% purity

93		4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,3-oxazol-2-yl}piperazine-1-carboxamide	From Example 18 Pale yellow solid Yield 7.20mg, 7.71% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₈ ClN ₇ O ₂ 424.1289 found 424.1288. HPLC: Rt 4.20min, 99.7% purity
94		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}-1,4-diazepane-1-carboxamide	From Intermediate 129 Pink solid Yield 56.7mg, 24.9% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₃ H ₂₂ FN ₇ O 432.1948 found 432.1955. HPLC: Rt 3.83min, 99.0% purity

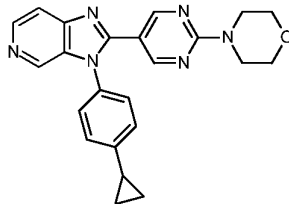
EXAMPLE 95

4-(5-{3-Phenyl-3H-imidazo[4,5-c]pyridin-2-yl}pyrimidin-2-yl)morpholine

- 5 Example 51 (115mg, 0.293mmol) was suspended in EtOH (5mL) and ammonium formate (148mg, 2.34mmol) and 10% Pd/C (50.0mg) were added. The reaction mixture was heated under reflux for 5h, filtered through Celite and concentrated *in vacuo*. The residue was dissolved in DCM (50mL), washed with 1M aq. Na₂CO₃ (50mL) dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by
- 10 column chromatography to give the title compound (40.2mg, 38.3%) as a white solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₀H₁₈N₆O 359.1620 found 359.1613. HPLC: Rt 4.65min, 99.8% purity.

EXAMPLE 96

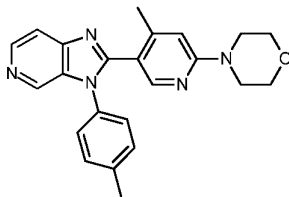
4-{5-[3-(4-Cyclopropylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine



Example 51 (250mg, 0.636mmol), cyclopropylboronic acid (54.7mg, 0.636mmol),
5 Pd(OAc)₂ (14.3mg, 63.6umol), XPhos (30.3mg, 63.6umol) and Cs₂CO₃ (518mg, 1.59mmol) were dissolved in dioxane (1.5mL) and water (1.5mL) and heated in a sealed tube at 100°C for 16h. The reaction mixture was partitioned between DCM (20mL) and water (20mL) and the organic fraction was washed with brine (20mL), dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by reverse
10 phase HPLC to give the title compound (17.1mg, 6.74%) as a white solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₃H₂₂N₆O 399.1933 found 399.1938. HPLC: Rt 5.16min, 99.4% purity.

EXAMPLE 97

15 **4-{4-Methyl-5-[3-(4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine**

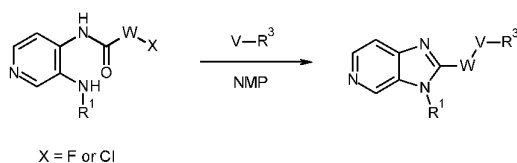


Intermediate 87 (300mg, 1.51mmol) was dissolved in NMP (2mL) and morpholine (783uL, 9.08mmol) and the reaction mixture was heated at 180°C in a microwave
20 reactor for 30min. The reaction mixture was diluted with EtOAc (10mL) and water (10mL). The organic fraction was washed with brine (10mL), dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by reverse phase HPLC to give the title compound (16.4mg, 2.81%) as a colourless gum. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₃H₂₃N₅O 386.1981 found 386.1982. HPLC: Rt 4.17min, 99.3% purity.

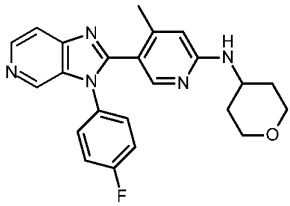
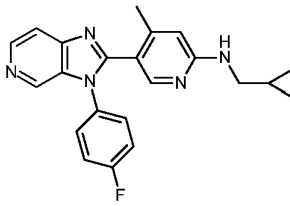
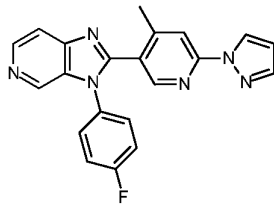
EXAMPLES 98-107

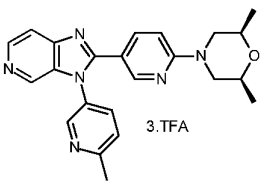
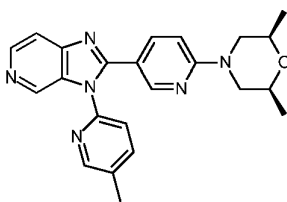
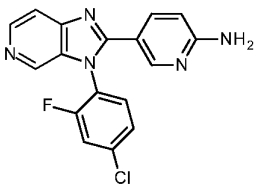
Examples 98-107 were prepared similarly to Example 97, by S_NAr and cyclisation of Intermediates 97-98, 106, 109-110, 112, 122 and 123 with the appropriate amine; see Table 15 below.

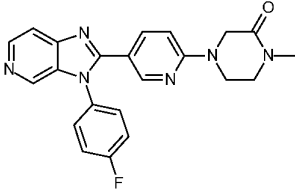
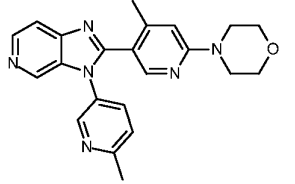
5 **Table 15: S_NAr and cyclisation of Intermediates 97-98, 106, 109-110, 112, 122 and 123**



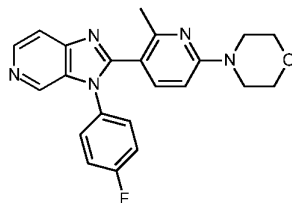
Ex	Structure	Name	Intermediate(s) used, Form, Yield, LCMS, HPLC
98		4-{3-Fluoro-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 97 White solid Yield 134mg, 27.7% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₇ F ₂ N ₅ O 394.1479 found 394.1478. HPLC: Rt 4.80min, 99.6% purity
99		5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-(morpholin-4-yl)-1,4-dihydropyridin-4-one	From Intermediate 98 White solid Yield 15.0mg, 1.11% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₈ FN ₅ O ₂ 392.1523 found 392.1520. HPLC: Rt 3.73min, 100% purity

100		5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methyl-N-(oxan-4-yl)pyridin-2-amine	From Intermediate 109 White solid Yield 26.0mg, 8.77% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₃ H ₂₂ FN ₅ O 404.1887 found 404.1892. HPLC: Rt 3.56min, 100% purity
101		N-(Cyclopropylmethyl)-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyridin-2-amine	From Intermediate 109 White solid Yield 43.0mg, 15.7% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₀ FN ₅ 374.1781 found 374.1787. HPLC: Rt 3.90min, 100% purity
102		5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methyl-2-(1H-pyrazol-1-yl)pyridine	From Intermediate 109 Off white solid Yield 28.1mg, 12.9% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₅ FN ₆ 371.1420 found 371.1419. HPLC: Rt 4.98min, 99.8% purity

103		(2R,6S)-2,6-Dimethyl-4-{5-[3-(6-methylpyridin-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine; tris(trifluoroacetic acid)	From Intermediate 110 Yellow gum Yield 26.0mg, 1.75% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₃H₂₄N₆O 401.2090 found 401.2084. HPLC: Rt 4.27min, 99.1% purity
104		(2R,6S)-2,6-Dimethyl-4-{5-[3-(5-methylpyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 112 White solid Yield 26.0mg, 3.71% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₃H₂₄N₆O 401.2090 found 401.2098. HPLC: Rt 4.66min, 98.9% purity
105		5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-amine	From Intermediate 106 Pale pink solid Yield 24.0mg, 8.49% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₇H₁₁ClFN₅ 340.0765 found 340.0773. HPLC: Rt 3.30min, 100% purity

106		4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}-1-methylpiperazin-2-one	From Intermediate 123 Pale yellow solid Yield 38.5mg, 13.1% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₁₉ FN ₆ O 403.1682 found 403.1684. HPLC: Rt 4.07min, 99.4% purity
107		4-{4-Methyl-5-[3-(6-methylpyridin-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine	From Intermediate 122 Pale yellow gum Yield 24.0mg, 3.11% LCMS (ES ⁺): 387.0 [MH] ⁺ HPLC: Rt 3.74min, 98.7% purity

EXAMPLE 108

4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-6-methylpyridin-2-yl}morpholine

5

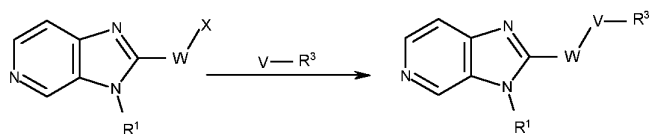
Intermediate 130 (94.0mg, 0.277mmol) was dissolved in DMA (1mL) and morpholine (192uL, 2.22mmol) was added. The reaction mixture was heated at 200°C in a microwave reactor for 30min and partitioned between DCM (20mL) and water (20mL). The organic fraction was washed with water (20mL), dried (MgSO₄)

10 and concentrated *in vacuo*. The residue was purified by reverse phase HPLC to give the title compound (47.0mg, 43.5%) as a white solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₂₀FN₅O 390.1730 found 390.1737. HPLC: Rt 3.96min, 99.7% purity.

EXAMPLES 109-111

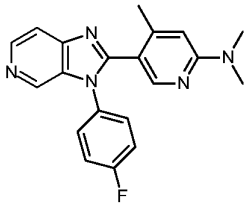
Examples 109-111 were prepared similarly to Example 108, by reaction of Intermediates 128, 131 and 133 with the appropriate amine; see Table 16 below.

Table 16: SNAr of Intermediates 128, 131 and 133 with the appropriate amine

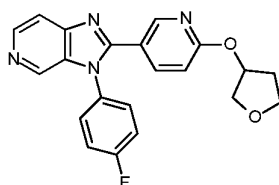


5

Ex	Structure	Name	Intermediate(s) used, Form, Yield, LCMS, HPLC
109		4-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N,N-dimethylpyridin-2-amine	From Intermediate 131 Yellow solid Yield 110mg, 53.4% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₆ FN ₅ 334.1468 found 334.1476. HPLC: Rt 3.19min, 99.7% purity
110		5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-amine	From Intermediate 128 White solid Yield 20.0mg, 26.2% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₇ H ₁₂ ClN ₅ 322.0859 found 322.0849. HPLC: Rt 3.45min, 99.7% purity

111		5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N,N,4-trimethylpyridin-2-amine	From Intermediate 133 Light yellow solid Yield 24.8mg, 29.2% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₈ FN ₅ 348.1624 found 348.1631. HPLC: Rt 3.44min, 99.1% purity
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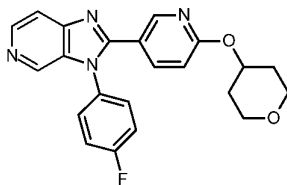
EXAMPLE 112

5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-(oxolan-3-yloxy)pyridine

5

NaH (14.8mg, 60% in mineral oil, 0.370mmol) was suspended in THF (1mL), 3-hydroxytetrahydrofuran (29.7uL, 0.370mmol) was added and the reaction mixture was stirred for 5min. Intermediate 127 (80.0mg, 0.246mmol) was added and the reaction mixture was stirred for 16h, quenched with water (20mL) and diluted with EtOAc (20mL). The organic fraction was washed with brine (20mL), dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by reverse phase HPLC to give the title compound (19.2mg, 20.7%) as a white solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₇FN₄O₂ 377.1414 found 377.1419. HPLC: Rt: 4.78min, 98.9% purity.

15 EXAMPLE 113

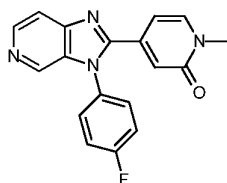
5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-(oxan-4-yloxy)pyridine

Example 113 was prepared similarly to Example 112, using 4-

hydroxytetrahydropyran instead of 3-hydroxytetrahydrofuran, to give the title compound (20.0mg, 20.8%) as a white solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₁₉FN₄O₂ 391.1570 found 391.1566. HPLC: Rt 5.04min, 99.7% purity.

5 EXAMPLE 114

4-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1-methyl-1,2-dihydropyridin-2-one

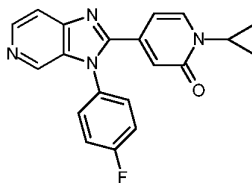


10 Intermediate 132 (26.0mg, 84.9μmol) and Cs₂CO₃ (55.3mg, 0.170mmol) were dissolved in dioxane (0.5mL), MeI (10.6μL, 0.170mmol) was added and the reaction mixture was stirred for 16h, filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC to give the title compound (1.41mg, 5.19%) as a white solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₁₈H₁₃FN₄O 321.1151 found 321.1156. HPLC: Rt 3.45min, 98.9% purity.

15

EXAMPLE 115

1-Cyclopropyl-4-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,2-dihydropyridin-2-one

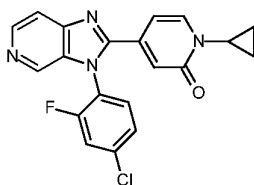


20 Intermediate 132 (120mg, 0.392mmol), cyclopropylboronic acid (101mg, 1.18mmol), Cu(OAc)₂ (110mg, 0.607mmol), 4,4'-dimethyl-2,2'-bipyridine (72.2mg, 0.392mmol) and Cs₂CO₃ (268mg, 0.823mmol) were suspended in dioxane (2.5mL) and the reaction mixture was stirred at 70°C for 6h. The reaction mixture was partitioned between EtOAc (25mL) and water (25mL) and the organic fraction was washed with
25 brine (25mL), dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by reverse phase HPLC to give the title compound (22.4mg, 16.5%) as an off white

solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₀H₁₅FN₄O 347.1308 found 347.1309. HPLC: Rt 3.88min, 100% purity.

EXAMPLE 116

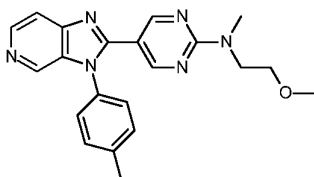
- 5 **4-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1-cyclopropyl-1,2-dihydropyridin-2-one**



- Example 116 was prepared similarly to Example 115, using Example 34 instead of
10 Intermediate 132, to give the title compound (31.0mg, 34.7%) as an off white solid. HRMS (ESI⁺) calcd for [MH]⁺ of C₂₀H₁₄ClFN₄O 381.0918 found 381.0922. HPLC: Rt 4.13min, 100% purity.

EXAMPLE 117

- 15 **N-(2-Methoxyethyl)-N-methyl-5-[3-(4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine**



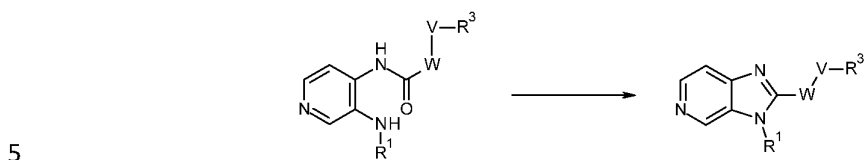
- Intermediate 107 (crude) was dissolved in NMP (2mL), Et₃N (633uL, 4.54mmol) was added and the reaction mixture was heated at 180°C in a microwave reactor for
20 30min. The reaction mixture was partitioned between DCM (15mL) and water (15mL) and the organic fraction was washed with brine (15mL), dried (MgSO₄) and concentrated *in vacuo*. The residue was triturated from MeOH to give the title compound as an off white solid (60.3mg, 10.6%). HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₂₂N₆O 375.1933 found 375.1942. HPLC: Rt: 4.99min, 99.3% purity.

25

EXAMPLES 118-119

Examples 118-119 were prepared similarly to Example 117, by cyclisation of Intermediates 111 and 113; see Table 17 below.

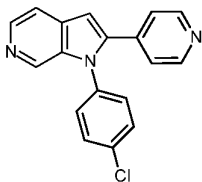
Table 17: Cyclisation of Intermediates 111 and 113



Ex	Structure	Name	Intermediate(s) used, Form, Yield, LCMS, HPLC
118		(2R,6S)-2,6-Dimethyl-4-{5-[3-(6-methylpyridin-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 111 White solid Yield 58.0mg, 7.23% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₃ N ₇ O 402.2042 found 402.2046. HPLC: Rt 4.52min, 97.6% purity
119		5-[3-(4-Methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-N-(oxan-4-yl)pyrimidin-2-amine; bis(trifluoroacetic acid)	From Intermediate 113 White solid Yield 12.0mg, 1.55% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₂ H ₂₂ N ₆ O 387.1933 found 387.1936. HPLC: Rt 4.42min, 99.4% purity

EXAMPLE 120

10 **4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridine**

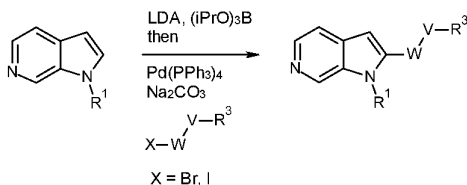


Intermediate 134 (100mg, 0.437mmol) and triisopropyl borate (212uL, 0.918mmol) were dissolved in THF (5mL) and the reaction mixture was cooled to 0°C. LDA (435uL, 2.0M in THF/heptane, 0.875mmol) was added and the reaction mixture was stirred at 0°C for 30min. The reaction was quenched with water (2mL) and diluted with dioxane (3mL). 4-Iodopyridine (108mg, 0.525mmol), Pd(PPh₃)₄ (40.4mg, 35.0umol) and a solution of Na₂CO₃ (139mg, 1.31mmol) in water (4mL) were added. The reaction mixture was heated using a microwave reactor at 160°C for 20min. The reaction mixture was partitioned between water (40mL) and EtOAc (40mL), and the organic fraction was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by reverse phase HPLC to give the title compound as a light yellow solid (21.8mg, 16.3%). HRMS (ESI⁺) calcd for [MH]⁺ of C₁₈H₁₂ClN₃ 306.0798 found 306.0809. HPLC: Rt 3.52min, 99.9% purity.

EXAMPLES 121-154

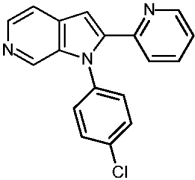
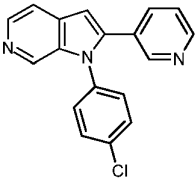
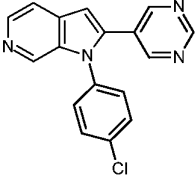
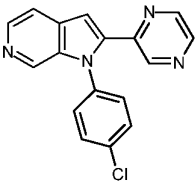
Examples 121-154 were prepared similarly to Example 120, by borate formation and Suzuki reaction of Intermediates 134-138 with the appropriate aryl or heteroaryl iodide or bromide; see Table 18 below.

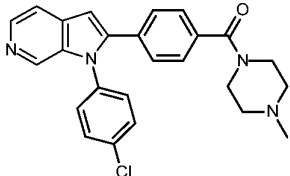
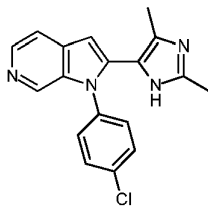
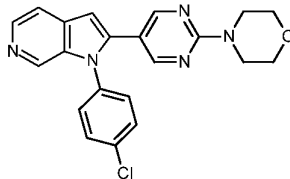
Table 18: Borate formation and Suzuki reactions of Intermediates 134-138

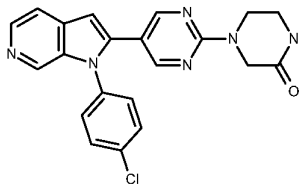
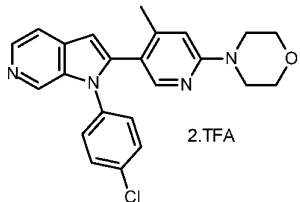
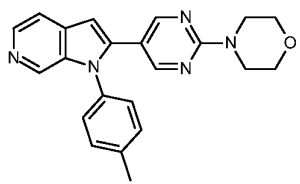


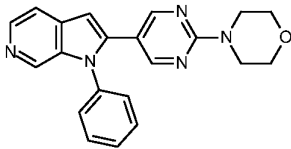
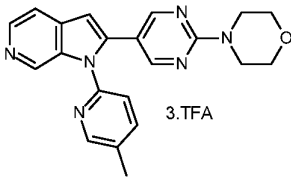
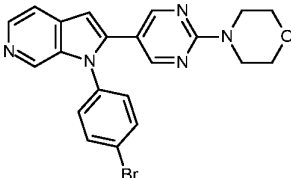
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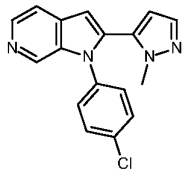
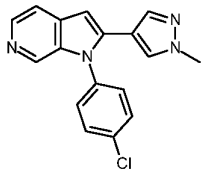
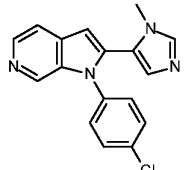
Ex	Structure	Name	Intermediate(s), Form, Yield, LCMS, HPLC
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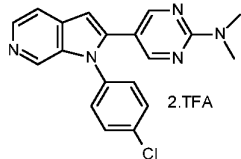
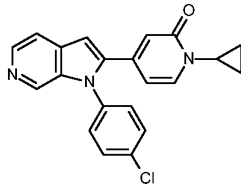
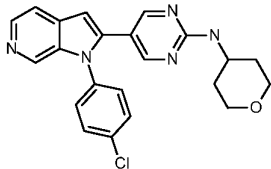
121		2-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridine	From Intermediate 134 Yellow gum Yield 14.0mg, 6.98% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₈ H ₁₂ ClN ₃ 306.0798 found 306.0811. HPLC: Rt 4.82min, 99.1% purity
122		3-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridine	From Intermediate 134 Yellow gum Yield 13.1mg, 9.80% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₈ H ₁₂ ClN ₃ 306.0798 found 306.0810. HPLC: Rt 3.95min, 99.1% purity
123		5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidine	From Intermediate 134 White solid Yield 64.9mg, 32.2% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₇ H ₁₁ ClN ₄ 307.0750 found 307.0753. HPLC: Rt 4.24min, 99.1% purity
124		2-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrazine	From Intermediate 134 Yellow gum Yield 28.0mg, 13.9% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₇ H ₁₁ ClN ₄ 307.0750 found 307.0764. HPLC: Rt 4.53min, 99.7% purity

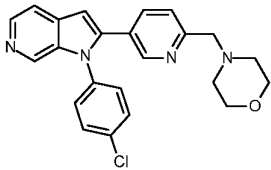
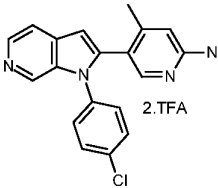
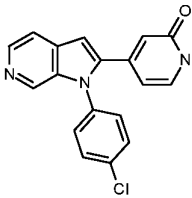
125		1-({4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]phenyl}carbonyl)-4-methylpiperazine	From Intermediate 134 and 139 Yellow solid Yield 23.0mg, 8.14% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₅ H ₂₃ ClN ₄ O 431.1638 found 431.1638. HPLC: Rt 3.77min, 97.9% purity
126		5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-2,4-dimethyl-1H-imidazole	From Intermediate 134 Off white solid Yield 14.6mg, 6.90% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₈ H ₁₅ ClN ₄ 323.1063 found 323.1067. HPLC: Rt 3.45min, 100% purity
127		4-{5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 134 Yellow solid Yield 67.2mg, 19.6% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₁ H ₁₈ ClN ₅ O 392.1278 found 392.1286. HPLC: Rt 5.12min, 100% purity

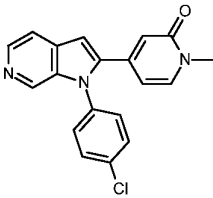
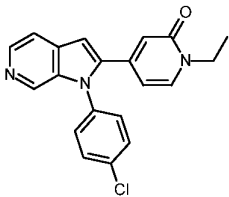
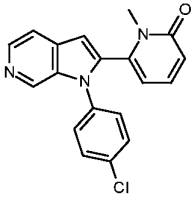
128		4-{5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}piperazin-2-one	From Intermediate 134 and 140 White solid Yield 71.5mg, 16.1% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₇ClN₆O 405.1230 found 405.1226. HPLC: Rt 4.23min, 98.6% purity.
129		4-{5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-4-methylpyridin-2-yl}morpholine; bis(trifluoroacetic acid)	From Intermediate 134 and 143 Colourless gum Yield 6.55mg, 0.95% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₃H₂₁ClN₄O 405.1482 found 405.1494. HPLC: Rt 4.06min, 98.6% purity.
130		4-{5-[1-(4-Methylphenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 135 White solid Yield 80.0mg, 17.9% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₂₁N₅O 372.1824 found 372.1828. HPLC: Rt 5.21min, 100% purity.

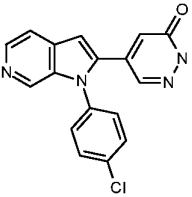
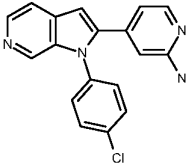
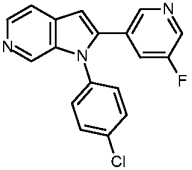
131		4-(5-{1-Phenyl-1H-pyrrolo[2,3-c]pyridin-2-yl}pyrimidin-2-yl)morpholine	From Intermediate 136 White solid Yield 58.5mg, 12.7% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₉N₅O 358.1668 found 358.1685. HPLC: Rt 4.90min, 97.4% purity.
132		4-{5-[1-(5-Methylpyridin-2-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}morpholine; tris(trifluoroacetic acid)	From Intermediate 137 Yellow solid Yield 3.35mg, 0.87% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₂₀N₆O 373.1777 found 373.1794. HPLC: Rt 4.68min, 99.6% purity.
133		4-{5-[1-(4-Bromophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}morpholine	From Intermediate 138 Light yellow solid Yield 38.0mg, 9.52% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₈BrN₅O 436.0773 found 436.0773. HPLC: Rt 5.32min, 96.2% purity.

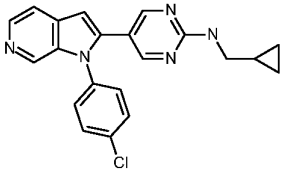
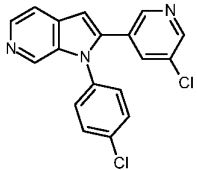
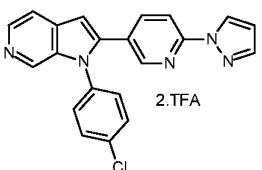
134		5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-methyl-1H-pyrazole	From Intermediate 134 Orange solid Yield 133mg, 32.8% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₇H₁₃ClN₄ 309.0907 found 309.0918. HPLC: Rt 4.64min, 98.4% purity.
135		4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-methyl-1H-pyrazole	From Intermediate 134 Orange solid Yield 153mg, 37.9% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₇H₁₃ClN₄ 309.0907 found 309.0910. HPLC: Rt 4.87min, 99.5% purity.
136		5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-methyl-1H-imidazole	From Intermediate 134 White solid Yield 63.8mg, 15.8% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₇H₁₃ClN₄ 309.0907 found 309.0914. HPLC: Rt 3.43min, 100% purity.

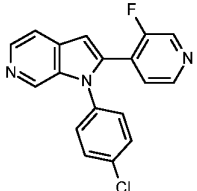
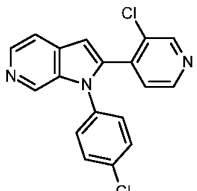
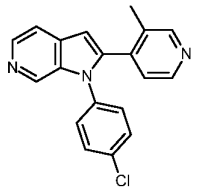
137		5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-N,N-dimethylpyrimidin-2-amine; bis(trifluoroacetic acid)	From Intermediate 134 Yellow gum Yield 142mg, 18.7% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₉H₁₆ClN₅ 350.1172 found 350.1180. HPLC: Rt 5.46min, 100% purity.
138		4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-cyclopropyl-1,2-dihydropyridin-2-one	From Intermediate 134 and 144 Yellow solid Yield 234mg, 36.9% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₆ClN₃O 362.1060 found 362.1063. HPLC: Rt 4.76min, 99.0% purity.
139		5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-N-(oxan-4-yl)pyrimidin-2-amine	From Intermediate 134 and 141 White solid Yield 122mg, 22.8% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₂H₂₀ClN₅O 406.1435 found 406.1435. HPLC: Rt 4.78min, 99.3% purity.

140		4-({5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridin-2-yl}methyl)morpholine	From Intermediate 134 and 145 Beige solid Yield 29.7mg, 4.20% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₃H₂₁ClN₄O 405.1482 found 405.1485. HPLC: Rt 3.91min, 98.0% purity.
141		5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-4-methylpyridin-2-amine; bis(trifluoroacetic acid)	From Intermediate 134 Colourless gum Yield 1.68mg, 0.34% LCMS (ES⁺): 335.1 [MH]⁺ HPLC: Rt 3.63min, 96.8% purity.
142		4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1,2-dihydropyridin-2-one	From Intermediate 134 Off white solid Yield 52.0mg, 14.8% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₈H₁₂ClN₃O 322.0747 found 322.0753. HPLC: Rt 3.75min, 97.6% purity.

143		4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-methyl-1,2-dihydropyridin-2-one	From Intermediate 134 and 146 Off white solid Yield 56.9mg, 15.5% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₄ ClN ₃ O 336.0904 found 336.0909. HPLC: Rt 4.07min, 98.6% purity.
144		4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-ethyl-1,2-dihydropyridin-2-one	From Intermediate 134 and 147 Off white solid Yield 59.5mg, 15.6% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₂₀ H ₁₆ ClN ₃ O 350.1060 found 350.1065. HPLC: Rt 4.39min, 100% purity.
145		6-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-methyl-1,2-dihydropyridin-2-one	From Intermediate 134 and 148 White solid Yield 82.2mg, 16.0% HRMS (ESI ⁺) calcd for [MH] ⁺ of C ₁₉ H ₁₄ ClN ₃ O 336.0904 found 336.0914. HPLC: Rt 4.20min, 99.5% purity.

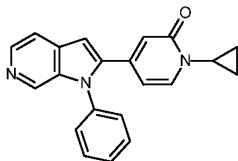
146		5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-2,3-dihydropyridazin-3-one	From Intermediate 134 Yellow solid Yield 35.5mg, 10.1% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₇H₁₁ClN₄O 323.0699 found 323.0700. HPLC: Rt 3.86min, 98.4% purity.
147		4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridin-2-amine	From Intermediate 134 Off white solid Yield 103mg, 29.4% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₈H₁₃ClN₄ 321.0907 found 321.0901. HPLC: Rt 3.56min, 100% purity.
148		3-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-5-fluoropyridine	From Intermediate 134 Yellow solid Yield 21.2mg, 6.00% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₈H₁₁ClFN₃ 324.0704 found 324.0714. HPLC: Rt 4.87min, 100% purity.

149		5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-N-(cyclopropylmethyl)pyrimidin-2-amine	From Intermediate 134 and 142 Off white solid Yield 32.0mg, 7.79% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₈ClN₅ 376.1329 found 376.1326. HPLC: Rt 5.38min, 99.1% purity.
150		3-Chloro-5-[1-(4-chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridine	From Intermediate 134 Off white solid Yield 19.2mg, 5.16% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₈H₁₁Cl₂N₃ 340.0408 found 340.0418. HPLC: Rt 5.17min, 100% purity.
151		5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-2-(1H-pyrazol-1-yl)pyridine; bis(trifluoroacetic acid)	From Intermediate 134 Yellow solid Yield 4.51mg, 0.69% HRMS (ESI⁺) calcd for [MH]⁺ of C₂₁H₁₄ClN₅ 372.1016 found 372.1025. HPLC: Rt 5.57min, 100% purity.

152		4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-3-fluoropyridine	From Intermediate 134 White solid Yield 9.24mg, 2.61% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₈H₁₁ClFN₃ 324.0704 found 324.0710. HPLC: Rt 4.74min, 100% purity.
153		3-Chloro-4-[1-(4-chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridine	From Intermediate 134 White solid Yield 40.1mg, 9.29% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₈H₁₁Cl₂N₃ 340.0408 found 340.0421. HPLC: Rt 4.98min, 100% purity.
154		4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-3-methylpyridine	From Intermediate 134 White solid Yield 29.5mg, 8.45% HRMS (ESI⁺) calcd for [MH]⁺ of C₁₉H₁₄ClN₃ 320.0954 found 320.0958. HPLC: Rt 3.71min, 100% purity.

EXAMPLE 155

1-Cyclopropyl-4-{1-phenyl-1H-pyrrolo[2,3-c]pyridin-2-yl}-1,2-dihydropyridin-2-one



Example 138 (50.0mg, 0.138mmol) was dissolved in MeOH (15mL) and passed
5 through an H-cube (70x4mm 10% Pd/C CatCart, 1.0mL/min, 30°C, 20bar). The
solvents were removed *in vacuo* and the residue purified by reverse phase HPLC to
give the title compound (0.610mg, 1.35%) as a colourless gum. LCMS (ES⁺): 328.0
[MH]⁺. HPLC: Rt 4.50min, 96.7% purity.

10 BIOLOGICAL TESTS

Biological Assays of the SSAO Enzyme Inhibitors

All primary assays were performed at RT. with purified recombinantly
expressed human SSAO. Enzyme was prepared essentially as described in Öhman
et al. (Protein Expression and Purification 46 (2006) 321–331). In addition,
15 secondary- and selectivity assays were performed using SSAO prepared from
various tissues or purified rat recombinant SSAO. The enzyme activity was assayed
with benzylamine as substrate by measuring either benzaldehyde production, using
¹⁴C-labeled substrate, or by utilizing the production of hydrogen peroxide in a
horseradish peroxidase (HRP) coupled reaction. Briefly, test compounds were
20 dissolved in dimethyl sulfoxide (DMSO) to a concentration of 10mM. Dose-response
measurements were assayed by either creating 1:10 serial dilutions in DMSO to
produce a 7 point curve or by making 1:3 serial dilutions in DMSO to produce 11
point curves. The top concentrations were adjusted depending on the potency of the
compounds and subsequent dilution in reaction buffer yielded a final DMSO
25 concentration ≤ 2%.

Hydrogen peroxide detection:

In a horseradish peroxidase (HRP) coupled reaction, hydrogen peroxide
oxidation of 10-acetyl-3,7-dihydroxyphenoxazine produced resorufin, which is a
highly fluorescent compound (Zhout and Panchuk-Voloshina. Analytical

Biochemistry 253 (1997) 169-174; Amplex[®] Red Hydrogen Peroxide/peroxidase Assay kit, Invitrogen A22188). Enzyme and compounds in 50mM sodium phosphate, pH 7.4 were set to pre-incubate in flat-bottomed microtiter plates for approximately 15min before initiating the reaction by addition of a mixture of HRP, benzylamine and Amplex reagent. Benzylamine concentration was fixed at a concentration corresponding to the Michaelis constant, determined using standard procedures. Fluorescence intensity was then measured at several time points during 1–2h, exciting at 544nm and reading the emission at 590nm. For the human SSAO assay final concentrations of the reagents in the assay wells were: SSAO enzyme 1ug/ml, benzylamine 100uM, Amplex reagent 20uM, HRP 0.1 U/mL and varying concentrations of test compound. The inhibition was measured as % decrease of the signal compared to a control without inhibitor (only diluted DMSO). The background signal from a sample containing no SSAO enzyme was subtracted from all data points. Data was fitted to a four parameter logistic model and IC₅₀ values were calculated using the GraphPad Prism 4 or XLfit 4 programs.

Aldehyde detection:

SSAO activity was assayed using ¹⁴C-labeled benzylamine and analysed by measuring radioactive benzaldehyde. In a white 96-well optiplate (Packard), 20uL of diluted test compound was pre-incubated at room temperature with 20uL SSAO enzyme for approximately 15min with continuous agitation. All dilutions were made with PBS. The reaction was initiated by adding 20uL of the benzylamine substrate solution containing [7-¹⁴C] Benzylamine hydrochloride (CFA589, GE Healthcare). The plate was incubated for 1h as above after which the reaction was stopped by acidification (10uL 1M aq HCl). Then 90uL Micro Scint-E solution (Perkin-Elmer) was added to each well and the plate was continuously mixed for 15min. Phase separation occurred instantly and activity was read in a Topcount scintillation counter (Perkin-Elmer). In the final reaction well, the human recombinant SSAO concentration was 10ug/ml. In order to optimize sensitivity, the substrate concentration was decreased as compared to the HRP coupled assay in order to get a higher fraction of radioactive product. In the human SSAO assay, benzylamine concentration was 40uM (0.2uCi/mL). Data was analysed as above.

All of the exemplified compounds of the invention had an IC₅₀ value of between 1nM and 1200nM at SSAO (see Table 19 below).

Table 19: SSAO inhibitory activity (A: <50nM, B: 50-200nM, C: 200-1200nM)

Compound	SSAO IC ₅₀ (nM)	Compound	SSAO IC ₅₀ (nM)	Compound	SSAO IC ₅₀ (nM)
1	C	53	C	105	C
2	C	54	C	106	B
3	B	55	A	107	A
4	A	56	C	108	C
5	B	57	B	109	C
6	C	58	C	110	C
7	B	59	B	111	C
8	A	60	B	112	A
9	A	61	A	113	A
10	B	62	B	114	C
11	A	63	C	115	A
12	B	64	C	116	B
13	A	65	A	117	C
14	C	66	B	118	A
15	B	67	A	119	B
16	C	68	A	120	C
17	C	69	A	121	A
18	B	70	A	122	B
19	B	71	C	123	A
20	B	72	C	124	A
21	A	73	B	125	C
22	A	74	C	126	A
23	A	75	A	127	A
24	A	76	B	128	A
25	A	77	C	129	A
26	B	78	A	130	B

27	A	79	A	131	C
28	B	80	B	132	B
29	C	81	A	133	A
30	C	82	A	134	A
31	C	83	A	135	A
32	A	84	A	136	A
33	C	85	A	137	A
34	B	86	A	138	A
35	C	87	A	139	A
36	B	88	A	140	A
37	A	89	A	141	B
38	B	90	A	142	B
39	A	91	C	143	A
40	B	92	A	144	B
41	A	93	B	145	A
42	B	94	C	146	B
43	A	95	B	147	A
44	C	96	B	148	A
45	C	97	C	149	A
46	A	98	B	150	B
47	A	99	A	151	B
48	A	100	C	152	C
49	A	101	B	153	B
50	A	102	B	154	A
51	A	103	B	155	C
52	A	104	A		

HERG ASSAY

Compounds of the invention were tested for inhibition of the human ether a go-go related gene (hERG) K⁺ channel using IonWorks patch clamp electrophysiology. 8

Point concentration-response curves were generated on two occasions using 3-fold serial dilutions from the maximum assay concentration (11uM). Electrophysiological recordings were made from a Chinese Hamster Lung cell line stably expressing the full length hERG channel. Single cell ion currents were measured in the perforated patch clamp configuration (100ug/mL amphotericin) at room temperature using an IonWorks Quattro instrument. The internal solution contained 140mM KCl, 1mM MgCl₂, 1mM EGTA and 20mM HEPES and was buffered to pH 7.3. The external solution contained 138mM NaCl, 2.7mM KCl, 0.9mM CaCl₂, 0.5mM MgCl₂, 8mM Na₂HPO₄ and 1.5mM KH₂PO₄, and was buffered to pH 7.3. Cells were clamped at a holding potential of 70mV for 30s and then stepped to +40mV for 1s. This was followed by a hyperpolarising step of 1s to 30mV to evoke the hERG tail current. This sequence was repeated 5 times at a frequency of 0.25Hz. Currents were measured from the tail step at the 5th pulse, and referenced to the holding current. Compounds were incubated for 6-7min prior to a second measurement of the hERG signal using an identical pulse train. A minimum of 17 cells were required for each pIC₅₀ curve fit. A control compound (quinidine) was used (see Table 20 below).

Table 20: hERG IC₅₀ (A: >10uM, B: 1-10uM, C: 0.1uM-1uM)

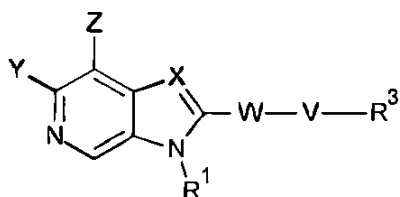
Compound	hERG IC ₅₀	Compound	hERG IC ₅₀	Compound	hERG IC ₅₀
2	A	57	A	98	A
3	A	63	A	110	A
4	B	64	A	117	A
9	B	67	B	120	B
11	A	69	A	122	B
12	A	70	A	127	C
13	A	71	A	128	A
18	A	75	A	130	C
20	A	77	A	131	B
21	A	78	A	132	C
23	A	80	A	136	B

24	A	81	A	138	B
46	A	82	A	139	C
47	B	85	A	140	B
48	B	86	A	142	B
50	A	88	B	147	B
51	B	89	A	152	B
52	A	91	A	153	B
53	A	92	A		
54	A	95	A		

AMENDED CLAIMS

received by the International Bureau on 17 July 2014 (17.07.2014)

1. A compound of formula (I) or a pharmaceutically acceptable salt, or N-oxide thereof:



(I)

Wherein:

Y is selected from hydrogen, hydroxyl, -NH₂, -NH-C₁₋₄-alkyl, -NH-halo-C₁₋₄-alkyl, or -C₁₋₄-alkoxy;

Z is selected from hydrogen, halogen, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, C₁₋₄-alkoxy, halo-C₁₋₄-alkoxy, -CONH₂, -SO₂NH₂, -NH₂, -NHC₁₋₄-alkyl, or -NHhalo-C₁₋₄-alkyl;

R¹ is a phenyl ring, or a 5 or 6-membered heteroaryl ring, either ring being optionally substituted with one or more substituents selected from halogen, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, a 3-7 membered cycloalkyl ring, -OR⁵, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, and -NR⁶S(O)₂R⁵; wherein

R^{4A}, R^{4B}, R⁵ and R⁶ are each independently selected from hydrogen, C₁₋₄-alkyl or halo-C₁₋₄-alkyl, or

R^{4A} and R^{4B} together with the nitrogen to which they are attached form a 3-7 membered cyclic amino group, optionally substituted by one or more substituents selected from: halogen, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, C₁₋₄-alkoxy, halo-C₁₋₄-alkoxy, -CONH₂, -SO₂NH₂, -NH₂, -NHC₁₋₄-alkyl, -NHhalo-C₁₋₄-alkyl;

X is -N=;

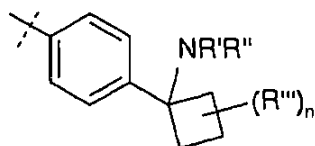
W is a phenyl ring or a 5 or 6-membered heteroaryl ring selected from pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, oxazolyl, thiazolyl or imidazolyl, any of which rings being optionally substituted with one or more substituents selected from halogen, cyano, oxo, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{7A}R^{7B}, -

$\text{NR}^6\text{C}(\text{O})\text{OR}^5$, $-\text{NR}^6\text{C}(\text{O})\text{R}^5$, $-\text{NR}^6\text{C}(\text{O})\text{NR}^{7A}\text{R}^{7B}$, $-\text{C}(\text{O})\text{NR}^{7A}\text{R}^{7B}$, $-\text{C}(\text{O})\text{R}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{SO}_2\text{R}^5$, $-\text{SO}_2\text{NR}^{7A}\text{R}^{7B}$ and $-\text{NR}^6\text{S}(\text{O})_2\text{R}^5$;

R^{7A} and R^{7B} are independently hydrogen, C_{1-4} -alkyl or halo- C_{1-4} -alkyl.

V is selected from a bond, $-\text{O}-$, $-\text{N}(\text{R}^6)-$, $-(\text{C}=\text{O})-$, $-\text{CONR}^6-$, $-\text{NR}^6\text{C}(\text{O})-$, or $-\text{C}_{1-4}$ -alkylene-, wherein the C_{1-4} -alkylene group is optionally substituted by halogen, and wherein any one of the carbon atoms of the C_{1-4} -alkylene group may be replaced by $-\text{O}-$ or $-\text{N}(\text{R}^6)-$;

R^3 is selected from hydrogen, $-\text{C}_{1-4}$ -alkyl, $-\text{C}_{1-4}$ -alkyl- C_{1-4} -alkoxy or a 3-7 membered heterocyclic ring or 3-7 membered cycloalkyl ring, or a 5 or 6-membered heteroaryl ring, any one of the rings being optionally substituted with one or more substituents selected from halogen, oxo, hydroxyl, cyano, C_{1-4} -alkyl, halo- C_{1-4} -alkyl, cyano- C_{1-4} -alkyl, $-\text{OR}^5$, $-\text{NR}^{4A}\text{R}^{4B}$, $-\text{NR}^6\text{C}(\text{O})\text{OR}^5$, $-\text{NR}^6\text{C}(\text{O})\text{R}^5$, $-\text{NR}^6\text{C}(\text{O})\text{NR}^{4A}\text{R}^{4B}$, $-\text{C}(\text{O})\text{NR}^{4A}\text{R}^{4B}$, $-\text{C}(\text{O})\text{R}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{SO}_2\text{R}^5$, $-\text{SO}_2\text{NR}^{4A}\text{R}^{4B}$ and $-\text{NR}^6\text{S}(\text{O})_2\text{R}^5$;
PROVIDED THAT groups $-\text{WVR}^3$ and/or R^1 are not:



15

wherein

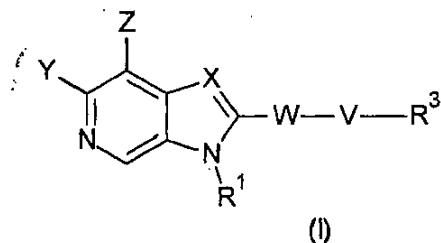
n is 0, 1, or 2;

R' and R'' are independently selected from the group consisting of H, $-\text{C}_1\text{-C}_6$ alkyl, $-(\text{C}=\text{O})-\text{C}_1\text{-C}_6$ alkyl and $-(\text{C}=\text{O})\text{OC}(\text{CH}_3)_3$; and

R''' is H, OH, or $\text{C}_1\text{-C}_6$ alkyl.

20

2. A compound of formula (I) or a pharmaceutically acceptable salt, or N-oxide thereof:



(I)

25

Wherein:

Y is selected from hydrogen, hydroxyl, -NH₂, -NH-C₁₋₄-alkyl, -NH-halo-C₁₋₄-alkyl, or -C₁₋₄-alkoxy;

Z is selected from hydrogen, halogen, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, C₁₋₄-alkoxy, halo-C₁₋₄-alkoxy, -CONH₂, -SO₂NH₂, -NH₂, -NHC₁₋₄-alkyl, or -NHhalo-C₁₋₄-alkyl;

R¹ is a phenyl ring, or a 5 or 6-membered heteroaryl ring, either ring being optionally substituted with one or more substituents selected from halogen, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, and -NR⁶S(O)₂R⁵; wherein
R^{4A}, **R^{4B}**, **R⁵** and **R⁶** are each independently selected from hydrogen, C₁₋₄-alkyl or halo-C₁₋₄-alkyl, or

R^{4A} and **R^{4B}** together with the nitrogen to which they are attached form a 3-7 membered cyclic amino group, optionally substituted by one or more substituents selected from: halogen, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, C₁₋₄-alkoxy, halo-C₁₋₄-alkoxy, -CONH₂, -SO₂NH₂, -NH₂, -NHC₁₋₄-alkyl, -NHhalo-C₁₋₄-alkyl;

X is -N=;

W is a phenyl ring or a 5 or 6-membered heteroaryl ring, either ring being optionally substituted with one or more substituents selected from halogen, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{7A}R^{7B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{7A}R^{7B}, -C(O)NR^{7A}R^{7B}, -C(O)R⁵, -C(O)OR⁵, -SO₂R⁵, -SO₂NR^{7A}R^{7B} and -NR⁶S(O)₂R⁵;

R^{7A} and **R^{7B}** are independently hydrogen, C₁₋₄-alkyl or halo-C₁₋₄-alkyl.

V is selected from a bond, -O-, -N(R⁶)-, -(C=O)-, -CONR⁶-, -NR⁶C(O)-, or -C₁₋₄-alkylene-, wherein the C₁₋₄-alkylene group is optionally substituted by halogen, and wherein any one of the carbon atoms of the C₁₋₄-alkylene group may be replaced by -O- or -N(R⁶)-;

R³ is hydrogen, or a 3-7 membered heterocyclic ring, or 3-7 membered cycloalkyl ring selected from cyclopropyl, cyclopentyl or cyclohexyl, or a 5 or 6-membered heteroaryl ring, any one of the rings being optionally substituted with one or more substituents selected from halogen, oxo, hydroxyl, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{4A}R^{4B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, -SO₂R⁵, -SO₂NR^{4A}R^{4B} and -NR⁶S(O)₂R⁵.

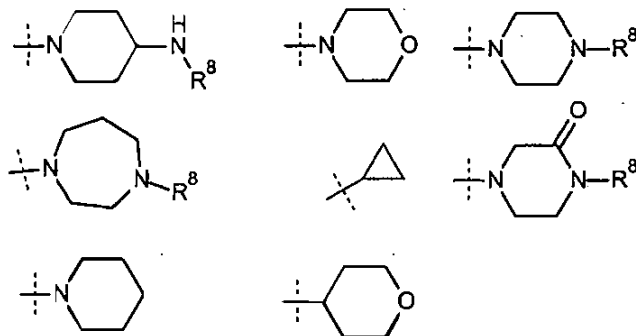
3. A compound according to claim 1 or 2 wherein Y is hydrogen.
4. A compound according to any one of claims 1 to 3 wherein Z is hydrogen.
- 5 5. A compound according to any one of claims 1 to 4 wherein R¹ is phenyl or 6-membered heteroaryl, optionally substituted with one or more substituents selected from halogen, C₁₋₄-alkyl or halo-C₁₋₄-alkyl.
- 10 6. A compound according to any one of claims 1 to 5 wherein R¹ is phenyl or pyridyl, optionally substituted with one or more substituents selected from F, Cl or CH₃.
- 15 7. A compound according to any one of claims 1 to 6 wherein W is a phenyl ring optionally substituted with one or more substituents as defined in claim 1 or claim 2.
- 18 8. A compound according to any one of claims 1 to 6 wherein W is a 6-membered heteroaryl ring selected from pyridine, pyridazine, pyrazine, or pyrimidine optionally substituted with one or more substituents as defined in claim 1 or claim 2.
- 20 9. A compound according to any one of claims 1 to 6 wherein W is a 5-membered heteroaryl ring selected from oxazole, thiazole or imidazole optionally substituted with one or more substituents as defined in claim 1 or claim 2.
- 25 10. A compound according to any one of claims 1 to 6 wherein W is an imidazolyl ring optionally substituted as in claim 1, and wherein the imidazolyl ring is connected to the pyrrolopyridine core via an imidazolyl ring carbon atom.
- 30 11. A compound according to any one of claims 1 to 10 wherein W is optionally substituted with one or more substituents selected from fluoro, chloro, cyano, CH₃ or CF₃.

12. A compound according to any one of claims 1 to 11 wherein V is $-\text{CH}_2-$, $-(\text{CH}_2)_2-$, or $-\text{N}(\text{R}^6)\text{CH}_2-$, or $-\text{CH}_2-\text{N}(\text{R}^6)-$.

13. A compound according to claim 1 or any one of claims 1 to 12 when dependent on claim 1 wherein R^3 is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted as defined in claim 1.

14. A compound according to any one of claims 1 to 11 wherein R^3 is formed from $-\text{NR}^{4A}\text{R}^{4B}$ wherein R^{4A} and R^{4B} , together with the nitrogen atom to which they are attached join together to form a 4-7 membered heterocyclic ring optionally substituted as defined in claim 1 or claim 2.

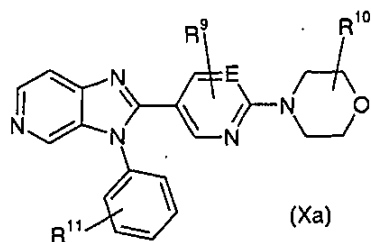
15. A compound according to any one of claims 1 to 11 wherein R^3 is selected from the group consisting of:



wherein R^8 is selected from hydrogen, CH_3 , $-\text{CONH}_2$, $-\text{NHCONH}_2$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{COCH}_3$.

16. A compound according to claim 1 wherein V is a direct bond.

17. A compound of formula (Xa)



wherein E is $-C=$ or $-N=$,

R^9 and R^{10} are each independently one or more substituents selected from hydrogen, halogen, cyano, oxo, C_{1-4} -alkyl, $-OC_{1-4}$ -alkyl, or halo- C_{1-4} -alkyl;

5 R^{11} is one or more substituents selected from hydrogen, halogen, cyano, cyclopropyl, C_{1-4} -alkyl, or halo- C_{1-4} -alkyl.

18. A compound according to claim 1 wherein R^1 is a phenyl ring, or a 5 or 6-membered heteroaryl ring, either ring being optionally substituted with one or more
10 3-7 membered cycloalkyl rings.

19. A compound according to claim 1 wherein W is a phenyl ring or a 5 or 6-membered heteroaryl ring, either ring being optionally substituted with one or more
15 oxo substituents.

20. A compound according to claim 1 wherein R^3 is selected from $-C_{1-4}$ -alkyl or $-C_{1-4}$ -alkyl- C_{1-4} -alkoxy.

21. A compound according to claim 1 or claim 2 selected from:
20 3-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridine (Example 1);
4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridine (Example 2);
4-[(5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl)methyl]morpholine (Example 3);
4-[6-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridazin-3-yl]morpholine
25 (Example 4);
4-[5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrazin-2-yl]morpholine (Example 5);
4-[(5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-

- yl)carbonyl)morpholine (Example 6);
5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N*-(oxan-4-yl)pyrazin-2-amine
(Example 7);
1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperidin-4-amine
5 (Example 8);
N-(Cyclopropylmethyl)-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-
2-amine (Example 9);
N-Cyclopropyl-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine
(Example 10);
10 5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N*-(oxan-4-yl)pyrimidin-2-amine
(Example 11);
4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}piperazin-2-one
(Example 12);
4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}piperazin-2-one
15 (Example 13);
5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N*-cyclopropylpyridine-2-
carboxamide (Example 14);
3-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-6-(oxan-4-yl)pyridazine
(Example 15);
20 *N*-(5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-
yl)methanesulfonamide (Example 16);
1-[4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,3-thiazol-2-yl]piperazine
(Example 17);
1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,3-oxazol-2-yl}piperazine
25 (Example 18);
1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,3-thiazol-2-yl}piperazine
(Example 19);
5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N*-(oxan-4-yl)pyrimidin-2-amine
(Example 20);
30 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyridin-2-
yl}morpholine (Example 21);
4-{5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyridin-2-
yl}morpholine (Example 22);

- (2R,6S)-4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}-2,6-dimethylmorpholine (Example 23);
- 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}-2,2-dimethylmorpholine (Example 24);
- 5 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}-1,4-oxazepane (Example 25);
- 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyrimidin-2-yl}morpholine (Example 26);
- 4-{5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyrimidin-2-yl}morpholine (Example 27);
- 10 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-6-methoxypyridin-2-yl}morpholine (Example 28);
- 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4,6-dimethylpyridin-2-yl}morpholine (Example 29);
- 15 2-Cyclopropyl-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidine (Example 30);
- 5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine (Example 31);
- 4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1-methyl-1,2-dihydropyridin-2-one (Example 32);
- 20 5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1-methyl-1,2-dihydropyridin-2-one (Example 33);
- 4-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,2-dihydropyridin-2-one (Example 34);
- 5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,2-dihydropyridin-2-one (Example 35);
- 25 (2R,6S)-2,6-Dimethyl-4-{5-[3-(5-methylpyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 36);
- N*-(3-Methoxypropyl)-5-[3-(4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine (Example 37);
- 30 5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N*-[2-(propan-2-yloxy)ethyl]pyrimidin-2-amine (Example 38);
- 5-[3-(4-Methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N*-[2-(propan-2-yloxy)ethyl]pyrimidin-2-amine (Example 39);

- 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}-1-methylpiperazin-2-one (Example 40);
- 4-{5-[3-(2,4-Difluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine (Example 41);
- 5 *N*-(2-Ethoxyethyl)-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine (Example 42);
- N*-(2-Ethoxyethyl)-5-[3-(4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine (Example 43);
- 5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1H-imidazole
- 10 (Example 44);
- 1-({3-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]phenyl)methyl}-4-methylpiperazine (Example 45);
- 1-({4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]phenyl)methyl}-4-methylpiperazine (Example 46);
- 15 4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine (Example 47);
- 1-({4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]phenyl)methyl}-1H-imidazole (Example 48);
- 4-({4-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]phenyl)methyl}morpholine
- 20 (Example 49);
- 1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperazine (Example 50);
- 4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 51);
- 25 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 52);
- 4-{5-[3-(2-Fluoro-4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 53);
- 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine
- 30 (Example 54);
- 4-{5-[3-(4-Fluoro-2-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 55);
- 4-{5-[3-(2-Chloro-4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-

- yl)morpholine (Example 56);
 4-{5-[3-(4-Methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine
 (Example 57);
 4-{5-[3-(6-Methylpyridin-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine
 5 (Example 58);
 4-{5-[3-(4-Bromophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine
 (Example 59);
 4-{5-[3-(2-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine
 (Example 60);
 10 4-{5-[3-(2-Chloro-4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-
 yl)morpholine (Example 61);
 4-{5-[3-(4-Fluoro-2-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-
 yl)morpholine (Example 62);
 4-{5-[3-(4-Methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine
 15 (Example 63);
 4-{5-[3-(6-Methylpyridin-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine
 (Example 64);
 4-{2-[6-(Morpholin-4-yl)pyridin-3-yl]-3H-imidazo[4,5-c]pyridin-3-yl}phenol (Example
 65);
 20 4-{5-[3-[4-(Trifluoromethyl)phenyl]-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-
 yl)morpholine (Example 66);
 4-{5-[3-(2-Fluoro-4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-
 yl)morpholine (Example 67);
 4-{5-[3-(2-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine
 25 (Example 68);
 5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-(pyrrolidin-1-yl)pyrimidine
 (Example 69);
 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}-2-
 methylmorpholine (Example 70);
 30 5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N,N*-dimethylpyridin-2-amine
 (Example 71);
 5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N,N*-dimethylpyrimidin-2-amine
 (Example 72);

- 4-{4-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine
(Example 73);
- 4-{5-[3-(4-Chloro-3-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine
(Example 74);
- 5 4-{5-[3-(5-Chloropyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine
(Example 75);
- 4-{5-[3-(5-Fluoropyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine
(Example 76);
- 10 4-{5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 77);
- 4-{5-[3-(2,4-Difluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine
(Example 78);
- 4-{5-[3-(5-Methylpyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine
(Example 79);
- 15 4-{5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine (Example 80);
- 4-{5-[3-(5-Chloropyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine
(Example 81);
- 20 4-{5-[3-(5-Methylpyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine
(Example 82);
- 5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-(pyrrolidin-1-yl)pyrimidine(Example 83);
- 5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N,N*-dimethylpyrimidin-2-amine(Example 84);
- 25 *N*-(1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl})piperidin-4-yl)acetamide (Example 85);
- 1-(4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl})piperazin-1-yl)ethan-1-one
(Example 86);
- 30 1-(4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl})-1,4-diazepan-1-yl)ethan-1-one; bis(trifluoroacetic acid)
(Example 87);

- N*-(1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperidin-4-yl)methanesulfonamide
(Example 88);
- 1-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}-4-methanesulfonylpiperazine
(Example 89);
- 4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperazine-1-carboxamide (Example 90);
- (1-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperidin-4-yl)urea (Example 91);
- 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}piperazine-1-carboxamide (Example 92);
- 4-{5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,3-oxazol-2-yl}piperazine-1-carboxamide (Example 93);
- 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}-1,4-diazepane-1-carboxamide (Example 94);
- 4-(5-[3-Phenyl-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl)morpholine (Example 95);
- 4-{5-[3-(4-Cyclopropylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 96);
- 4-(4-Methyl-5-[3-(4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl)morpholine (Example 97);
- 4-(3-Fluoro-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl)morpholine (Example 98);
- 5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-(morpholin-4-yl)-1,4-dihydropyridin-4-one (Example 99);
- 5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methyl-*N*-(oxan-4-yl)pyridin-2-amine (Example 100);
- N*-(Cyclopropylmethyl)-5-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methylpyridin-2-amine (Example 101);
- 5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-4-methyl-2-(1H-pyrazol-1-yl)pyridine (Example 102);

- (2R,6S)-2,6-Dimethyl-4-{5-[3-(6-methylpyridin-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine (Example 103);
- (2R,6S)-2,6-Dimethyl-4-{5-[3-(5-methylpyridin-2-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine (Example 104);
- 5 5-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-amine (Example 105);
- 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}-1-methylpiperazin-2-one (Example 106);
- 4-{4-Methyl-5-[3-(6-methylpyridin-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-yl}morpholine (Example 107);
- 10 4-{5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-6-methylpyridin-2-yl}morpholine (Example 108);
- 4-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N,N*-dimethylpyridin-2-amine (Example 109);
- 15 5-[3-(4-Chlorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyridin-2-amine (Example 110);
- 5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N,N*,4-trimethylpyridin-2-amine (Example 111);
- 5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-(oxolan-3-yloxy)pyridine (Example 112);
- 20 5-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-2-(oxan-4-yloxy)pyridine (Example 113);
- 4-[3-(4-Fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1-methyl-1,2-dihydropyridin-2-one (Example 114);
- 1-Cyclopropyl-4-[3-(4-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1,2-dihydropyridin-2-one (Example 115);
- 25 4-[3-(4-Chloro-2-fluorophenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-1-cyclopropyl-1,2-dihydropyridin-2-one (Example 116);
- N*-(2-Methoxyethyl)-*N*-methyl-5-[3-(4-methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-amine (Example 117);
- 30 (2R,6S)-2,6-Dimethyl-4-{5-[3-(6-methylpyridin-3-yl)-3H-imidazo[4,5-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 118);
- 5-[3-(4-Methylphenyl)-3H-imidazo[4,5-c]pyridin-2-yl]-*N*-(oxan-4-yl)pyrimidin-2-amine

and pharmaceutically acceptable salts thereof.

22. A pharmaceutical composition comprising a compound according to any one
5 of claims 1 to 21, and one or more suitable excipients.

23. A compound according to any one of claims 1 to 21 for use in the treatment
of inflammation, an inflammatory disease, an immune or an autoimmune disorder, or
inhibition of tumour growth.

10

24. A method for the treatment of inflammation, an inflammatory disease, an
immune or an autoimmune disorder, or inhibition of tumour growth, which comprises
administering to a subject suffering such disease an effective amount of a
compound of formula (I) as claimed in any of claims 1 to 21.

15

25. A compound according to claim 23 or method according to claim 24 wherein
the inflammation or inflammatory disease or immune or autoimmune disorder is
arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis
and psoriatic arthritis), synovitis, vasculitis, Sjogren's disease, a condition
20 associated with inflammation of the bowel (including Crohn's disease, ulcerative
colitis, inflammatory bowel disease and irritable bowel syndrome), atherosclerosis,
multiple sclerosis, Alzheimer's disease, vascular dementia, Parkinson's disease,
cerebral amyloid angiopathy, cerebral autosomal dominant arteriopathy with
subcortical infarcts and leukoencephalopathy, a pulmonary inflammatory disease
25 (including asthma, chronic obstructive pulmonary disease and acute respiratory
distress syndrome), a fibrotic disease (including idiopathic pulmonary fibrosis,
cardiac fibrosis, liver fibrosis and systemic sclerosis (scleroderma)), an inflammatory
disease of the skin (including contact dermatitis, atopic dermatitis and psoriasis), an
inflammatory disease of the eye (including age related macular degeneration, uveitis
30 and diabetic retinopathy), systemic inflammatory response syndrome, sepsis, an
inflammatory and/or autoimmune condition of the liver (including autoimmune
hepatitis, primary biliary cirrhosis, alcoholic liver disease, sclerosing cholangitis, and
autoimmune cholangitis), diabetes (type I or II) and/or the complications thereof,

chronic heart failure, congestive heart failure, an ischemic disease (including stroke and ischemia-reperfusion injury) or myocardial infarction and/or the complications thereof, or epilepsy.

- 5 26. A compound according to claim 23 or method according to claim 24 for treatment of a disease selected from rheumatoid arthritis, osteoarthritis, liver fibrosis, chronic obstructive pulmonary disease, multiple sclerosis, Sjogren's disease, Alzheimer's disease, Parkinson's disease, inflammatory bowel disease, or vascular dementia.

10

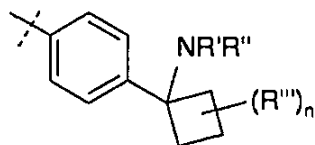
27. A compound of formula (I), or a pharmaceutically acceptable salt, or N-oxide thereof wherein:

X is $-C(R^2)=$;

- 15 R^2 is selected from hydrogen, halogen, cyano, C_{1-4} -alkyl, halo- C_{1-4} -alkyl, cyano- C_{1-4} -alkyl, $-OR^5$, $-NR^{4A}R^{4B}$, $-NR^6C(O)OR^5$, $-NR^6C(O)R^5$, $-NR^6C(O)NR^{4A}R^{4B}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)R^5$, $-C(O)OR^5$, $-SO_2R^5$, $-SO_2NR^{4A}R^{4B}$ and $-NR^6S(O)_2R^5$;

Y, Z, R^1 , W, V, R^3 are as defined in claim 1,

PROVIDED THAT groups $-WVR^3$ and/or R^1 are not: and



20

wherein

n is 0, 1, or 2;

R' and R'' are independently selected from the group consisting of H, $-C_1-C_6$ alkyl, $-(C=O)-C_1-C_6$ alkyl and $-(C=O)OC(CH_3)_3$; and

- 25 R''' is H, OH, or C_1-C_6 alkyl.

28. A compound of formula (I), or a pharmaceutically acceptable salt, or N-oxide thereof wherein:

X is $-C(R^2)=$;

R² is selected from hydrogen, halogen, cyano, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, cyano-C₁₋₄-alkyl, -OR⁵, -NR^{4A}R^{4B}, -NR⁶C(O)OR⁵, -NR⁶C(O)R⁵, -NR⁶C(O)NR^{4A}R^{4B}, -C(O)NR^{4A}R^{4B}, -C(O)R⁵, -C(O)OR⁵, -SO₂R⁵, -SO₂NR^{4A}R^{4B} and -NR⁶S(O)₂R⁵; and Y, Z, R¹, W, V, R³ are as defined in claim 2.

- 5 29. A compound according to claim 27 or claim 28 selected from:
- 4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridine (Example 120);
- 2-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridine (Example 121);
- 3-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridine (Example 122);
- 10 5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidine (Example 123);
- 2-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrazine (Example 124);
- 1-((4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]phenyl)carbonyl)-4-methylpiperazine (Example 125);
- 5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-2,4-dimethyl-1H-imidazole
- 15 (Example 126);
- 4-{5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 127);
- 4-{5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}piperazin-2-one (Example 128);
- 20 4-{5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-4-methylpyridin-2-yl}morpholine (Example 129);
- 4-{5-[1-(4-Methylphenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 130);
- 4-{5-[1-Phenyl-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example
- 25 131);
- 4-{5-[1-(5-Methylpyridin-2-yl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 132);
- 4-{5-[1-(4-Bromophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyrimidin-2-yl}morpholine (Example 133);
- 30 5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-methyl-1H-pyrazole (Example 134);
- 4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-methyl-1H-pyrazole (Example 135);

- 5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-methyl-1H-imidazole (Example 136);
- 5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-*N,N*-dimethylpyrimidin-2-amine (Example 137);
- 5 4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-cyclopropyl-1,2-dihydropyridin-2-one (Example 138);
- 5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-*N*-(oxan-4-yl)pyrimidin-2-amine (Example 139);
- 4-({5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridin-2-yl)methyl)morpholine (Example 140);
- 10 5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-4-methylpyridin-2-amine (Example 141);
- 4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1,2-dihydropyridin-2-one (Example 142);
- 15 4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-methyl-1,2-dihydropyridin-2-one (Example 143);
- 4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-ethyl-1,2-dihydropyridin-2-one (Example 144);
- 6-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-1-methyl-1,2-dihydropyridin-2-one (Example 145);
- 20 5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-2,3-dihydropyridazin-3-one (Example 146);
- 4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridin-2-amine (Example 147);
- 3-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-5-fluoropyridine (Example 148);
- 25 5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-*N*-(cyclopropylmethyl)pyrimidin-2-amine (Example 149);
- 3-Chloro-5-[1-(4-chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridine (Example 150);
- 5-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-2-(1H-pyrazol-1-yl)pyridine (Example 151);
- 30 4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-3-fluoropyridine (Example 152);
- 3-Chloro-4-[1-(4-chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]pyridine (Example 153);
- 4-[1-(4-Chlorophenyl)-1H-pyrrolo[2,3-c]pyridin-2-yl]-3-methylpyridine (Example 154);

1-Cyclopropyl-4-(1-phenyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-1,2-dihydropyridin-2-one
(Example 155); or
a pharmaceutically acceptable salt thereof.

5 30. A pharmaceutical composition comprising a compound according to any one of claims 26 to 29, and one or more suitable excipients.

31. A compound according to any one of claims 26 to 29 for use in the treatment
of inflammation, an inflammatory disease, an immune or an autoimmune disorder, or
10 inhibition of tumour growth.

32. A method for the treatment of inflammation, an inflammatory disease, an
immune or an autoimmune disorder, or inhibition of tumour growth, which comprises
administering to a subject suffering such disease an effective amount of a
15 compound of formula (I) as claimed in any of claims 26 to 29.

33. A compound according to claim 31 or method according to claim 32 wherein
the inflammation or inflammatory disease or immune or autoimmune disorder is
arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis
20 and psoriatic arthritis), synovitis, vasculitis, Sjogren's disease, a condition
associated with inflammation of the bowel (including Crohn's disease, ulcerative
colitis, inflammatory bowel disease and irritable bowel syndrome), atherosclerosis,
multiple sclerosis, Alzheimer's disease, vascular dementia, Parkinson's disease,
cerebral amyloid angiopathy, cerebral autosomal dominant arteriopathy with
25 subcortical infarcts and leukoencephalopathy, a pulmonary inflammatory disease
(including asthma, chronic obstructive pulmonary disease and acute respiratory
distress syndrome), a fibrotic disease (including idiopathic pulmonary fibrosis,
cardiac fibrosis, liver fibrosis and systemic sclerosis (scleroderma)), an inflammatory
disease of the skin (including contact dermatitis, atopic dermatitis and psoriasis), an
30 inflammatory disease of the eye (including age related macular degeneration, uveitis
and diabetic retinopathy), systemic inflammatory response syndrome, sepsis, an
inflammatory and/or autoimmune condition of the liver (including autoimmune
hepatitis, primary biliary cirrhosis, alcoholic liver disease, sclerosing cholangitis, and

autoimmune cholangitis), diabetes (type I or II) and/or the complications thereof, chronic heart failure, congestive heart failure, an ischemic disease (including stroke and ischemia-reperfusion injury) or myocardial infarction and/or the complications thereof, or epilepsy.

5

34. A compound according to claim 31 or method according to claim 32 for treatment of a disease selected from rheumatoid arthritis, osteoarthritis, liver fibrosis, chronic obstructive pulmonary disease, multiple sclerosis, Sjogren's disease, Alzheimer's disease, Parkinson's disease, inflammatory bowel disease, or

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vascular dementia.