New pyrimidine derivatives and their use in therapy as well as the use of pyrimidine derivatives in the manufacture of a medicament for prevention and/or treatment of Alzheimer's disease.

TECHNICAL FIELD OF INVENTION

The present invention relates to new compounds of formula **I**, as a free base or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, to pharmaceutical formulations containing said compounds and to the use of said compounds in therapy. The present invention further relates to a process for the preparation of compounds of formula **I** and to new intermediates used therein.

BACKGROUND OF THE INVENTION

Glycogen synthase kinase 3 (GSK3) is a serine / threonine protein kinase composed of two isoforms (α and β), which are encoded by distinct genes but are highly homologous within the catalytic domain. GSK3 is highly expressed in the central and peripheral nervous system. GSK3 phosphorylates several substrates including tau, ß-catenin, glycogen synthase, pyruvate dehydrogenase and elongation initiation factor 2b (eIF2b). Insulin and growth factors activate protein kinase B, which phosphorylates GSK3 on serine 9 residue and inactivates it.

Alzheimer's Disease (AD) dementias, and taupathies

AD is characterized by cognitive decline, cholinergic dysfunction and neuronal death, neurofibrillary tangles and senile plaques consisting of amyloid-β deposits. The sequence of these events in AD is unclear, but they are believed to be related. Glycogen synthase kinase 3β (GSK3β) or Tau (τ) phosphorylating kinase selectively phosphorylates the microtubule associated protein τ in neurons at sites that are hyperphosphorylated in AD brains. Hyperphosphorylated protein τ has lower affinity for microtubules and accumulates as paired helical filaments, which are the main components that constitute neurofibrillary tangles and neuropil threads in AD brains. This results in depolymerization of microtubules, which leads to dying back of axons and neuritic dystrophy. Neurofibrillary tangles are consistently found in diseases such as AD, amyotrophic lateral sclerosis, parkinsonism-dementia of Gaum, corticobasal degeneration, dementia pugilistica and head trauma, Down's syndrome, postencephalatic parkinsonism, progressive supranuclear palsy, Niemann-Pick's Disease and Pick's Disease. Addition of amyloid-β to primary

hippocampal cultures results in hyperphosphorylation of τ and a paired helical filaments-like state via induction of GSK3β activity, followed by disruption of axonal transport and neuronal death (Imahori and Uchida., J. Biochem 121:179-188, 1997). GSK3β preferentially labels neurofibrillary tangles and has been shown to be active in pre-tangle neurons in AD brains. GSK3 protein levels are also increased by 50% in brain tissue from AD patients. Furthermore, GSK3β phosphorylates pyruvate dehydrogenase, a key enzyme in the glycolytic pathway and prevents the conversion of pyruvate to acetyl-Co-A (Hoshi et al., PNAS 93:2719-2723, 1996). Acetyl-Co-A is critical for the synthesis of acetylcholine, a neurotransmitter with cognitive functions. Thus, GSK3β inhibition may have beneficial effects in progression as well as the cognitive deficits associated with Alzheimer's disease and other above-referred to diseases.

Chronic and Acute Neurodegenerative Diseases

Growth factor mediated activation of the PI3K /Akt pathway has been shown to play a key role in neuronal survival. The activation of this pathway results in GSK3β inhibition. Recent studies (Bhat et. al., PNAS 97:11074-11079 (2000)) indicate that GSK3β activity is increased in cellular and animal models of neurodegeneration such as cerebral ischemia or after growth factor deprivation. For example, the active site phosphorylation was increased in neurons vulnerable to apoptosis, a type of cell death commonly thought to occur in chronic and acute degenerative diseases such as Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, Huntington's Disease and HIV dementia, ischemic stroke and head trauma. Lithium was neuroprotective in inhibiting apoptosis in cells and in the brain at doses that resulted in the inhibition of GSK3β. Thus GSK3β inhibitors could be useful in attenuating the course of neurodegenerative diseases.

Bipolar Disorders (BD)

Bipolar Disorders are characterised by manic episodes and depressive episodes. Lithium has been used to treat BD based on its mood stabilising effects. The disadvantage of lithium is the narrow therapeutic window and the danger of overdosing that can lead to lithium intoxication. The recent discovery that lithium inhibits GSK3 at therapeutic concentrations has raised the possibility that this enzyme represents a key target of lithium's action in the brain (Stambolic et al., Curr. Biol. 6:1664-1668, 1996; Klein and Melton; PNAS 93:8455-8459, 1996). Inhibition of GSK3β may therefore be of therapeutic relevance in the treatment of BD as well as in AD patients that have affective disorders.

Schizophrenia

GSK3 is involved in signal transduction cascades of multiple cellular processes, particularly during neural development. Kozlovsky et al (Am J Psychiatry 2000 May;157(5):831-3) found that GSK3β levels were 41% lower in the schizophrenic patients than in comparison subjects. This study indicates that schizophrenia involves neurodevelopmental pathology and that abnormal GSK3 regulation could play a role in schizophrenia. Furthermore, reduced β-catenin levels have been reported in patients exhibiting schizophrenia (Cotter et al., Neuroreport 9:1379-1383 (1998)).

Diabetes

Insulin stimulates glycogen synthesis in skeletal muscles via the dephosphorylation and thus activation of glycogen synthase. Under resting conditions, GSK3 phosphorylates and inactivates glycogen synthase via dephosphorylation. GSK3 is also over-expressed in muscles from Type II diabetic patients (Nikoulina et al., Diabetes 2000 Feb;49(2):263-71). Inhibition of GSK3 increases the activity of glycogen synthase thereby decreasing glucose levels by its conversion to glycogen. GSK3 inhibition may therefore be of therapeutic relevance in the treatment of Type I and Type II diabetes and diabetic neuropathy.

Hair Loss

GSK3 phosphorylates and degrades β-catenin. β-catenin is an effector of the pathway for keratonin synthesis. β-catenin stabilisation may be lead to increase hair development. Mice

expressing a stabilised β-catenin by mutation of sites phosphorylated by GSK3 undergo a process resembling de novo hair morphogenesis (Gat et al., Cell 1998 Nov 25;95 (5):605-14)). The new follicles formed sebaceous glands and dermal papilla, normally established only in embryogenesis. Thus GSK3 inhibition may offer treatment for baldness.

Oral contraceptives

Vijajaraghavan et al. (Biol Reprod 2000 Jun; 62 (6):1647-54) reported that GSK3 is high in motile versus immotile sperm. Immunocytochemistry revealed that GSK3 is present in the flagellum and the anterior portion of the sperm head. These data suggest that GSK3 could be a key element underlying motility initiation in the epididymis and regulation of mature sperm function. Inhibitors of GSK3 could be useful as contraceptives for males.

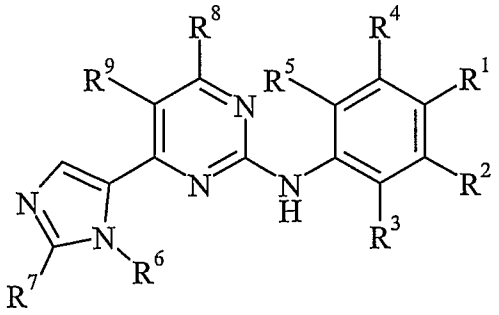
Bone-related disorders

It has been shown that GSK3 inhibitors could be used for treatment of bone-related disorders. This has been discussed in e.g. Tobias et al., *Expert Opinion on Therapeutic Targets*, Feb 2002, pp 41-56.

DISCLOSURE OF THE INVENTION

The object of the present invention is to provide compounds having a selective inhibiting effect at GSK3 as well as having a good bioavailability.

The present invention therefore relates to the use of a compound of the formula **I**:



I

wherein

R^1 is selected from hydrogen, halo, cyano, NO_2, C_{1-3}alkyl, C_{1-3}haloalkyl, OR^a, $SO_2NR^bR^c$, C_{0-2}alkylC(O)NR^bR^c, C_{1-4}alkylNR^bR^c, CH_2OR^h, SO_2R^i, C(O)OR^a, CH(OH)R^j and C(O)R^j;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, $SO_2NR^bR^c$, C(O)NR^bR^c, $CH_2NR^bR^c$, CH_2OR^h, SO_2R^i, C(O)OR^a and C(O)R^j; or

R^1 and R^2, together with the atoms to which they are attached join to form a 5- or 6-membered heterocyclic ring containing at least one N, O or S, in which any of the hydrogens of the CH_2-groups within the said heterocyclic ring can be substituted with oxo, hydroxy or halo and in which any sulphur atom within said heterocyclic ring is optionally oxidised to -SO_2-;

R^3 and R^5 are independently selected from hydrogen, halo, cyano, C_{1-3}alkyl, C_{1-3}haloalkyl and OR^a;

R^6 is selected from CH_3, C_6alkyl, C_6alkenyl, C_6alkynyl and C_6haloalkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^7 is selected from hydrogen, C_{1-3}alkyl, cyano, and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more OR^a;

R^8 and R^9 are independently selected from hydrogen, cyano and halo;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl and C_{1-6}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-6}haloalkyl is optionally substituted with one or more C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy,

cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a;

R^d and R^e are independently selected from hydrogen, C_{1-6}alkyl and C_{1-6}haloalkyl, wherein said C_{1-6}alkyl or C_{1-6}haloalkyl is optionally substituted with one or more OR^a; or

R^d and R^e may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^h is hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

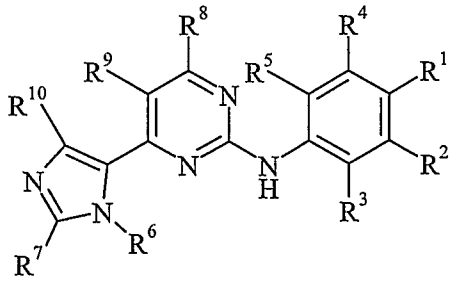
R^i is selected from C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl and C_{1-3}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-3}haloalkyl is optionally substituted with one or more halo, cyano, di-(C_{1-4}alkyl)amino-, C_{1-3}haloalkyl, C_{1-3}alkyl, heterocyclyl or OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl, OR^a, halo or cyano;

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof;

in the manufacture of a medicament for prevention and/or treatment of dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica.

The present invention also relates to the use of a compound of the formula **Ia**:



Ia

wherein

R^1 is selected from hydrogen, halo, cyano, NO_2, C_{1-3}alkyl, C_{1-3}haloalkyl, OR^a, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, CH_2OR^h, SO_2R^i and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-3}alkyl, C_{1-3}haloalkyl, OR^a, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, CH_2OR^h, SO_2R^i and $C(O)R^j$;

R^3 and R^5 independently are selected from hydrogen, C_{1-3}alkyl, C_{1-3}haloalkyl and OR^a;

R^6 is selected from CH_3, C_6alkyl, C_6alkenyl, C_6alkynyl, and C_6haloalkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^7 is selected from C_{1-3}alkyl, cyano, and C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more OR^a;

R^8 and R^9 are independently selected from hydrogen, cyano and halo;

R^{10} is hydrogen;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl or C_{1-6}haloalkyl, wherein aid C_{1-6}alkyl or C_{1-6}haloalkyl is optionally substituted with one or more OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-3}alkyl or C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^d and R^e are independently selected from hydrogen, C_{1-6}alkyl or C_{1-6}haloalkyl, said C_{1-6}alkyl or C_{1-6}haloalkyl is optionally substituted with one or more OR^a; or

R^d and R^e may, together with the atom to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-3}alkyl or

C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^h is hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy

R^i is C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl, OR^a, halo or cyano;
as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof;
in the manufacture of a medicament for prevention and/or treatment of dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica.

One embodiment of the present invention relates to the use of a compound according to formula **I** or formula **Ia**, wherein

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, SO_2R^i and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-3}haloalkyl, OR^a, $C(O)NR^bR^c$, and SO_2R^i;

R^3 and R^5 independently are selected from hydrogen, C_{1-3}alkyl, and OR^a;

R^6 is selected from CH_3, C_6alkyl and C_6haloalkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^7 is selected from C_{1-3}alkyl, cyano, and C_{1-3}haloalkyl;

R^{10} is hydrogen;

R^8 and R^9 independently are selected from hydrogen, cyano and halo;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl or C_{1-6}haloalkyl, said C_{1-6}alkyl or C_{1-6}haloalkyl is optionally substituted with one or more OR^a; or

R^b and R^c may, together with the atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-3}alkyl or C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^i is C_{1-3}alkyl or C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more OR^a;

R^j is an arylor heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl, OR^a, halo or cyano;
as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

One embodiment of the present invention provides the use of the compound according to formula **I** or formula **Ia** wherein R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl; as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

Another embodiment of the present invention provides the use of the compound of formula **I** or formula **Ia**, wherein R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, SO_2R^i and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-3}haloalkyl, OR^a, $C(O)NR^bR^c$ and SO_2R^i;

R^3 and R^5 independently are selected from hydrogen, C_{1-3}alkyl, and OR^a;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl;

R^7 is selected from C_{1-3}alkyl and C_{1-3}haloalkyl;

R^{10} is hydrogen;

R^8 and R^9 independently are selected from hydrogen and halo;

R^a is C_{1-3}alkyl or C_{1-3}haloalkyl;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, said C_{1-6}alkyl optionally substituted with one or more OR^a or

R^b and R^c may, together with the atom to which they are attached, together form a 4-, 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more halo or C_{1-3}alkyl;

R^i is C_{1-3}alkyl;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl, OR^a, halo or cyano

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

Yet another additional embodiment of the present invention provides the use of the compound according to formula **I**, wherein

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, C_{0-2}alkylC(O)NR^bR^c, C_{1-4}alkylNR^bR^c, SO_2R^i, $C(O)OR^a$, $CH(OH)R^j$ and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, SO_2R^i, $C(O)NR^bR^c$ and $C(O)OR^a$; or

R^1 and R^2, together with the atoms to which they are attached join to form a 5- or 6-membered heterocyclic ring containing at least one N, O or S, in which any of the hydrogen sof the CH_2-groups within the said heterocyclic ring can be substituted with oxo, hydroxy or halo and in which any sulphur atom within said heterocyclic ring is optionally oxidised to $-SO_2-$;

R^3 and R^5 are independently selected from hydrogen, C_{1-3}alkyl, and OR^a;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N or O, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl;

R^7 is selected from C_{1-3}alkyl, cyano, and C_{1-3}haloalkyl;

R^8 and R^9 are independently selected from hydrogen and halo;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl and heterocyclyl, wherein said C_{1-6}alkyl, heterocyclyl is optionally substituted with one or more cyano, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a;

R^d and R^e are independently selected from hydrogen and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more OR^a; or

R^d and R^e may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo;

R^i is selected from C_{1-6}alkyl and heterocyclyl, wherein said C_{1-6}alkyl or heterocyclyl is optionally substituted with one or more di-(C_{1-4}alkyl)amino-, heterocyclyl or OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl;
as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

A further embodiment of the present invention relates to the use of a compound according to formula **I**, wherein R^3 and R^5 are hydrogen.

Yet a further embodiment of the present invention relates to the use of a compound according to formula **I**, wherein R^8 is hydrogen and R^9 is hydrogen or fluoro.

Another embodiment of the present invention relates to the use of a compound according to formula **I**, wherein R^6 is C_6alkyl. One additional embodiment of the present invention provides the use of a compound according to formula **I**, wherein R^6 is tetrahydropyran.

Yet one additional embodiment of the present invention provides the use of a compound according to formula **I**, wherein R^7 is methyl or trifluoromethyl.

One embodiment of the present invention provides the use of a compound according to formula **I**, wherein R^4 is selected from hydrogen, halo, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, SO_2R^i, $C(O)NR^bR^c$ and $C(O)OR^a$. According to one additional embodiment of the present invention, R^4 is $C(O)NR^bR^c$ and R^b and R^c are independently selected from hydrogen and C_{1-6}alkyl, and said C_{1-6}alkyl is optionally substituted with one or more OR^a and and R^a is C_{1-3}alkyl. According to a further embodiment of the present invention, R^4 is trifluoromethyl. According to yet another embodiment of the present invention R^4 is chloro. According to a further embodiment of the present invention, R^a is trifluoromethyl.

Another embodiment of the present invention relates to the use of a compound according to formula **I**, wherein R^2 is hydrogen, halo, C_{1-3}alkyl or OR^a. According to one additional embodiment of the present invention, R^2 is chloro.

Yet another embodiment of the present invention provides the use of a compound according to formula **I**, wherein R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, C_{0-2}alkyl$C(O)NR^bR^c$, C_{1-4}alkylNR^bR^c, SO_2R^i, $C(O)OR^a$, $CH(OH)R^j$ and $C(O)R^j$. According to one additional embodiment of the present invention, R^1 is C_{0-2}alkyl$C(O)NR^bR^c$ and R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl andC_{1-6}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-6}haloalkyl is optionally substituted with one or more C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^dR^e; or R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said

heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a. According to one additional embodiment of the present invention R^b and R^c, together with the atom to which they are attached, form a heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a. According to yet one additional embodiment of the present invention said heterocyclic ring is substituted with methyl.

According to another embodiment of the present invention, R^1 is C_{1-4}alkylNR^bR^c and R^b and R^c together with the atom to which they are attached, form a heterocyclic ring.

According to yet another embodiment of the present invention R^1 is SO_2R^i and R^i is C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more OR^a. According to one additional embodiment of the present invention R^i is methyl. According to one additional embodiment of the present invention, R^1 is $SO_2NR^bR^c$ and R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl andC_{1-6}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-6}haloalkyl is optionally substituted with one or more C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^dR^e; or R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a. According to a further additional embodiment of the present invention, R^b and R^c, together with the atom to which they are attached form a heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-6}alkyl or C_{1-3}haloalkyl. According to a further embodiment of the present invention said heterocyclic ring is substituted with a C_{1-6}alkyl. According to a further embodiment of the present invention said C_{1-6}alkyl is methyl.

One embodiment of the present invention relates to the the use of a compound according to formula **I**, wherein said compound is selected from:

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[3-methoxy-5-(trifluoromethyl)phenyl]pyrimidin-2-amine;

N-(3,5-Dichlorophenyl)-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(phenyl)methanone;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]-3-nitrophenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-[(4-methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{3-methoxy-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-[(4-methylpiperazin-1-yl)carbonyl]-3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-[(4-methylpiperazin-1-yl)sulfonyl]-3-(trifluoromethoxy)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

[4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)phenyl](pyridin-2-yl)methanone hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(trifluoromethyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

3-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzonitrile hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(pyridin-2-yl)methanone hydrochloride;

4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzonitrile hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(piperazin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

N-{4-[(Dimethylamino)methyl]phenyl}-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(1-morpholin-4-ylethyl)phenyl]pyrimidin-2-amine;

N-[4-(1-Azetidin-1-ylethyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(2-morpholin-4-ylethyl)phenyl]pyrimidin-2-amine;

N-[4-(Methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{4-[(4-Methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{4-[(4-Methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

4-[2-Methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine;

4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(morpholin-4-ylsulfonyl)phenyl]pyrimidin-2-amine;

N-(4-{[4-(2-Methoxyethyl)piperazin-1-yl]sulfonyl}phenyl)-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{4-[(4-Isopropylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

4-[2-Methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine;

(N-(1-Methylpiperidin-4-yl)-4-({4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzenesulfonamide;

N-{4-[(4-Methyl-1,4-diazepan-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N,N-Diethyl-4-({4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzenesulfonamide;

N-[4-(Azetidin-1-ylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{3-[(4-Methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{3-Chloro-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{3-Methyl-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-N-(4-{[(3R)-3-methylmorpholin-4-yl]sulfonyl}phenyl)-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-N-{3-methyl-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-N-(4-{[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]sulfonyl}phenyl)-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)-N,N-dimethylbenzenesulfonamide;

N-[4-(Azetidin-1-ylsulfonyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

Methyl 3-{[4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}benzoate;

3-[[4-(2,3-Dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-N-(3-methoxypropyl)benzamide hydrochloride;

[4-[[4-(2,3-Dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-2-(trifluoromethoxy)phenyl]-(4-methylpiperazin-1-yl)methanone hydrochloride;

N-[4-(Azetidin-1-ylcarbonyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

N-{4-[(3,3-Difluoroazetidin-1-yl)carbonyl]phenyl}-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-N-[3-methyl-4-(morpholin-4-ylmethyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-N-[4-(morpholin-4-ylmethyl)phenyl]-4-[3-oxan-4-yl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-amine hydrochloride;

5-Fluoro-N-{4-[(4-fluoropiperidin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

Ethyl 4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzoate;

N,N-Diethyl-4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-(3-methoxypropyl)benzamide hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-(1,4-oxazepan-4-yl)methanone hydrochloride;

(4-ethylpiperazin-1-yl)-[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-methanone hydrochloride;

(2,6-dimethylmorpholin-4-yl)-[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-methanone hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-(3-fluoropyrrolidin-1-yl)-methanone hydrochloride;

(3,3-difluoropyrrolidin-1-yl)-[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-methanone hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-methyl-benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-tetrahydropyran-4-yl-benzamide hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-(3-hydroxypyrrolidin-1-yl)-methanone hydrochloride;

N-(2-cyanoethyl)-4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-methyl-benzamide hydrochloride;

N-ethyl-4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-(2-hydroxyethyl)benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-(2-hydroxyethyl)-N-methyl-benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-(2-hydroxyethyl)benzamide hydrochloride;

N-(2-dimethylaminoethyl)-4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-benzamide hydrochloride;

(4-dimethylamino-1-piperidyl)-[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-methanone hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-[4-(2-methoxyethyl)piperazin-1-yl]-methanone hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-[2-(1-piperidyl)ethyl]benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-(2-morpholinoethyl)benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-isopropyl-benzamide hydrochloride;

N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-benzamide hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-(4-isopropylpiperazin-1-yl)-methanone hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-(4-methyl-1,4-diazepan-1-yl)-methanone hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-tetrahydrofuran-3-yl-benzamide hydrochloride;

5-Fluoro-N-[4-(methylsulfonyl)phenyl]-4-[1-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-[4-(Azetidin-1-ylcarbonyl)phenyl]-5-fluoro-4-[1-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-[4-(Azetidin-1-ylcarbonyl)-3-chlorophenyl]-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

N-[4-(Azetidin-1-ylcarbonyl)-3-methylphenyl]-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

N-[3-Chloro-4-(methylsulfonyl)phenyl]-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoro-N-[4-(methylsulfonyl)phenyl]pyrimidin-2-amine;

N-{3-Chloro-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoro-N-{3-methyl-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine;

N-[4-(Azetidin-1-ylcarbonyl)-3-(trifluoromethoxy)phenyl]-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

5-Fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]-pyrimidin-2-amine hydrochloride;

[4-[5-Fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-yl]aminophenyl]-(4-methylpiperazin-1-yl)-methanone hydrochloride;

[4-[5-Fluoro-4-[3-tetrahydropyran-4-yl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-yl]aminophenyl]-(4-methylpiperazin-1-yl)-methanone hydrochloride;

5-Fluoro-N-[3-(methylsulfonyl)-4-(morpholin-4-ylmethyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-N-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

6-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)-2,3-dihydro-4H-thiochromen-4-one 1,1-dioxide hydrochloride;

6-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)thiochroman-4-ol 1,1-dioxide hydrochloride;

N-(3-Dimethylaminopropyl)-3-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]benzamide;

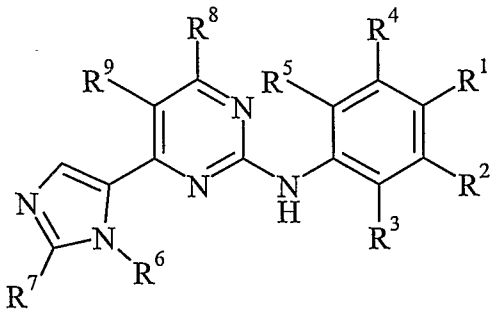
N-(3-Dimethylaminopropyl)-3-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-N-methyl-benzamide hydrochloride;

[3-[[4-(2,3-Dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]-[3-(hydroxymethyl)-1-piperidyl]methanone;

N-{3-Chloro-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;
5-Fluoro-N-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;
(4-{[4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(pyridin-2-yl)methanol;
5-Fluoro-N-[4-(isopropylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;
N-[4-(Ethylsulfonyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;
5-Fluoro-N-{4-[(2-methoxyethyl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;
N-(4-{[2-(Diethylamino)ethyl]sulfonyl}phenyl)-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;
2-{[4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)phenyl]sulfonyl}ethanol;
{5-Fluoro-4-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-pyrimidin-2-yl}-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-amine;
5-{5-Fluoro-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenylamino]-pyrimidin-4-yl}-1-(tetrahydro-pyran-4-yl)-1H-imidazole-2-carbonitrile; and
{5-Fluoro-4-[2-methyl-3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-pyrimidin-2-yl}-[4-(tetrahydro-pyran-2-ylmethanesulfonyl)-phenyl]-amine.
in the manufacture of a medicament for prevention and/or treatment of dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica.

According to one embodiment of the present invention, the disease is Alzheimer's Disease.

The present invention also relates to a compound of the formula **I**:



I

wherein

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, OR^a, $SO_2NR^bR^c$, C_{0-2}alkylC(O)NR^bR^c, C_{1-4}alkylNR^bR^c, CH_2OR^h, SO_2R^i, C(O)OR^a, CH(OH)R^j and C(O)R^j;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, C(O)NR^bR^c, SO_2R^i and C(O)OR^a; or

R^1 and R^2, together with the atoms to which they are attached form a 5- or 6-membered heterocyclic ring containing at least one N, O or S, in which any of the hydrogens of the CH_2-groups within said heterocyclic ring can be substituted with oxo, hydroxy or halo and in which any sulphur atom within said heterocyclic ring is optionally oxidised to -SO_2-;

R^3 and R^5 are independently selected from hydrogen, C_{1-3}alkyl and OR^a;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^7 is selected from hydrogen, C_{1-3}alkyl, cyano and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more OR^a;

R^8 and R^9 are independently are selected from hydrogen and halo;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl andC_{1-6}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-}

$_6$haloalkyl is optionally substituted with one or more C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a;

R^d and R^e are independently selected from hydrogen, C_{1-6}alkyl and C_{1-6}haloalkyl, wherein said C_{1-6}alkyl or C_{1-6}haloalkyl is optionally substituted with one or more OR^a; or

R^d and R^e may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

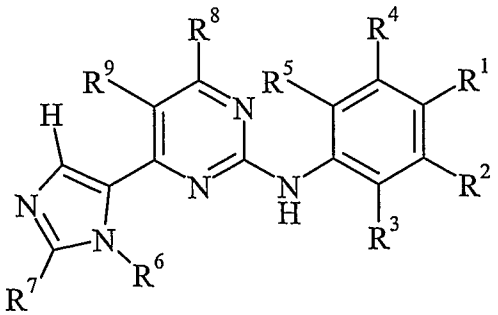
R^h is hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^i is selected from C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl and C_{1-3}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-3}haloalkyl is optionally substituted with one or more halo, cyano, di-(C_{1-4}alkyl)amino-, C_{1-3}haloalkyl, C_{1-3}alkyl, heterocyclyl or OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl, OR^a, halo or cyano;

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

The present invention also relates to a compound of the formula **Ib**:



Ib

wherein

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, CH_2OR^h, SO_2R^i and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-3}haloalkyl, OR^a, $C(O)NR^bR^c$, and SO_2R^i;

R^3 and R^5 independently are selected from hydrogen, C_{1-3}alkyl, and OR^a;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl;

R^7 is selected from C_{1-3}alkyl and C_{1-3}haloalkyl;

R^8 and R^9 independently are selected from hydrogen and halo;

R^a is C_{1-3}alkyl or C_{1-3}haloalkyl;

R^b and R^c are independently selected from hydrogen and C_{1-6}alkyl, optionally substituted with one or more OR^a; or

R^b and R^c may, together with the atom to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from N or O, wherein said heterocyclic ring is optionally substituted with one or more halo or C_{1-3}alkyl ;

R^h is hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^i is C_{1-3}alkyl;

R^j is an aryl or heteroaryl ring;

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

One embodiment of the present invention relates to a compound of formula **I**, wherein

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, C_{0-2}alkyl$C(O)NR^bR^c$, C_{1-4}alkylNR^bR^c, SO_2R^i, $C(O)OR^a$, $CH(OH)R^j$ and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, SO_2R^i, $C(O)NR^bR^c$ and $C(O)OR^a$; or

R^1 and R^2, together with the atoms to which they are attached join to form a 5- or 6-membered heterocyclic ring containing at least one N, O or S, in which any of the hydrogens of the CH_2-groups within the said heterocyclic ring can be substituted with oxo, hydroxy or halo and in which any sulphur atom within said heterocyclic ring is optionally oxidised to $-SO_2-$;

R^3 and R^5 are independently selected from hydrogen, C_{1-3}alkyl, and OR^a;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N or O, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl;

R^7 is selected from C_{1-3}alkyl, cyano, and C_{1-3}haloalkyl;

R^8 and R^9 are independently selected from hydrogen and halo;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl and heterocyclyl, wherein said C_{1-6}alkyl, heterocyclyl is optionally substituted with one or more cyano, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a;

R^d and R^e are independently selected from C_{1-6}alkyl; or

R^d and R^e may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo;

R^i is selected from C_{1-6}alkyl and heterocyclyl, wherein said C_{1-6}alkyl or heterocyclyl is optionally substituted with one or more di-(C_{1-4}alkyl)amino-, heterocyclyl or OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl;
as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

Another embodiment of the present invention relates to a compound of formula **I**, wherein R^3 and R^5 are hydrogen.

Yet another embodiment of the present invention provides a compound of formula **I**, wherein R^8 is hydrogen and R^9 is hydrogen or fluoro.

A further embodiment of the present invention provides a compound of formula **I**, wherein R^6 is C_6alkyl. According to one additional embodiment of the present invention, R^6 is tetrahydropyran.

Yet another embodiment of the present invention provides a compound of formula **I**, wherein R^7 is methyl or trifluoromethyl.

One embodiment of the present invention provides a compound of formula **I**, wherein R^4 is selected from hydrogen, halo, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, SO_2R^i, $C(O)NR^bR^c$ and $C(O)OR^a$. According to another embodiment of the present invention, R^b and R^c are independently selected from hydrogen and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more OR^a and wherein R^a is C_{1-3}alkyl. According to yet another embodiment of the present invention, R^4 is trifluoromethyl. According to one additional embodiment of the present invention, R^4 is chloro. According to yet one additional embodiment of the present invention, R^a is trifluoromethyl.

One embodiment of the present invention provides a compound of formula **I**, wherein R^2 is hydrogen, halo, C_{1-3}alkyl or OR^a. According to one additional embodiment of the present invention, R^2 is chloro.

Yet one embodiment of the present invention provides a compound of formula **I**, wherein R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, C_{0-2}alkyl$C(O)NR^bR^c$, C_{1-}

$_4$alkylNR^{b}R^c, SO$_2$R^i, C(O)OR^a, CH(OH)R^j and C(O)R^j. According to one additional embodiment of the present invention ,R^1 is C$_{0-2}$alkylC(O)NR^{b}R^c and R^b and R^c are independently selected from hydrogen, C$_{1-6}$alkyl, heterocyclyl, aryl, heteroaryl andC$_{1-6}$haloalkyl, wherein said C$_{1-6}$alkyl, heterocyclyl, aryl, heteroaryl or C$_{1-6}$haloalkyl is optionally substituted with one or more C$_{1-4}$alkyl, C$_{1-4}$haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^{d}R^e; or R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C$_{1-4}$alkyl)amino-, C$_{1-6}$alkyl or C$_{1-3}$haloalkyl, wherein said C$_{1-6}$alkyl or C$_{1-3}$haloalkyl is optionally further substituted with one or more C$_{1-3}$alkoxy or OR^a. According to yet one additional embodiment of the present invention R^b and R^c, together with the atom to which they are attached, form a heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or more halo, C$_{1-6}$alkyl or C$_{1-3}$haloalkyl, wherein said C$_{1-6}$alkyl or C$_{1-3}$haloalkyl is optionally further substituted with one or more C$_{1-3}$alkoxy or OR^a. According to another embodiment of the present invention, said heterocyclic ring is substituted with methyl.

According to a further embodiment of the present invention, R^1 is C$_{1-4}$alkylNR^{b}R^c and R^b and R^c together with the atom to which they are attached, form a heterocyclic ring.

According to yet a further embodiment of the present invention, SO$_2$R^i and R^i is C$_{1-6}$alkyl, wherein said C$_{1-6}$alkyl is optionally substituted with one or more OR^a. Accoding to yet one additional embodiment of the present invention R^i is methyl.

According to another embodiment of the present invention, R^1 is SO$_2$NR^{b}R^c and R^b and R^c are independently selected from hydrogen, C$_{1-6}$alkyl, heterocyclyl, aryl, heteroaryl andC$_{1-6}$haloalkyl, wherein said C$_{1-6}$alkyl, heterocyclyl, aryl, heteroaryl or C$_{1-6}$haloalkyl is optionally substituted with one or more C$_{1-4}$alkyl, C$_{1-4}$haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^{d}R^e; or R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C$_{1-4}$alkyl)amino-, C$_{1-6}$alkyl or C$_{1-}$

$_3$haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a. According to one additional embodiment of the present invention, R^b and R^c together with the atom to which they are attached form a heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-6}alkyl or C_{1-3}haloalkyl. According to yet one additional embodiment of the present invention said heterocyclic ring is substituted with a C_{1-6}alkyl. According to yet a further additional embodiment of the present invention, said C_{1-6}alkyl is methyl.

One embodiment of the present inevntion provides a compound of formula **I** selected from:

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[3-methoxy-5-(trifluoromethyl)phenyl]pyrimidin-2-amine;

N-(3,5-Dichlorophenyl)-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(phenyl)methanone;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]-3-nitrophenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-[(4-methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{3-methoxy-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-[(4-methylpiperazin-1-yl)carbonyl]-3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-[(4-methylpiperazin-1-yl)sulfonyl]-3-(trifluoromethoxy)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

[4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)phenyl](pyridin-2-yl)methanone hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(trifluoromethyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

3-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzonitrile hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}pyrimidin-2-amine hydrochloride;
4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;
(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(pyridin-2-yl)methanone hydrochloride;
4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzonitrile hydrochloride;
5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(piperazin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride; and
5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride.

One embodiment of the present invention relates to the compounds disclosed above for use in therapy.

The present invention also relates to a compound selected from:
2-Chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine;
2-Methyl-4-[(4-methylpiperazin-1-yl)carbonyl]aniline;
4-[(4-Methylpiperazin-1-yl)carbonyl]-3-nitroaniline;
4-[(4-Methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)aniline;
4-[*N*-Acetyl-*N*-(tetrahydro-2*H*-pyran-4-yl)]amino-5-methylisoxazole;
5-Acetyl-2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazole;
(2*E*)-3-Dimethylamino-1-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;
(2*Z*)-3-Dimethylamino-2-fluoro-1-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;
5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;
1-(4-Chloro-2-methoxybenzoyl)-4-methylpiperazine;
1-[4-Bromo-2-(methylsulfonyl)benzoyl]-4-methylpiperazine;
4-(*N*-Acetyl-*N*-cyclohexyl)amino-5-methylisoxazole;
5-Acetyl-1-cyclohexyl-2-methyl-1*H*-imidazole;

(2*E*)-3-Dimethylamino-1-(1-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one;
(2*Z*)-3-Dimethylamino-2-fluoro-1-(1-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one;
4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine;
5-Acetyl-2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazole;
(2*E*)-3-Dimethylamino-1-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;
(2*Z*)-3-Dimethylamino-2-fluoro-1-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;
5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;
4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine;
1-(tert-Butoxycarbonyl)-4-(4-bromo-benzenesulfonyl)-piperazine;
5-Acetyl-1-(tetrahydro-2*H*-pyran-4-yl)- 2-trifluoromethyl-1*H*-imidazole;
(2*E*)-3-Dimethylamino-1-[1-(tetrahydro-2*H*-pyran-4-yl)-2-trifluoromethyl-1*H*-imidazol-5-yl]prop-2-en-1-one;
(2*Z*)-3-Dimethylamino-2-fluoro-1-[1-(tetrahydro-2*H*-pyran-4-yl)-2-trifluoromethyl-1*H*-imidazol-5-yl]prop-2-en-1-one;
5-Fluoro-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;
4-[2-Methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;
1-[(4-Bromo-2-chlorophenyl)sulfonyl]-4-methylpiperazine;
(3*R*)-4-[(4-Bromophenyl)sulfonyl]-3-methylmorpholine;
(1*S*,4*S*)-2-[(4-Bromophenyl)sulfonyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane;
Methyl 4-bromo-2-(trifluoromethoxy)benzoate;
4-Bromo-2-(trifluoromethoxy)benzoic acid;
4-(4-Chloro-2-methylbenzyl)morpholine;
Lithium 4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzoate;
1-(4-Bromo-2-methylbenzoyl)azetidine;
4-Bromo-2-(trifluoromethoxy)benzoic acid;
1-[4-Bromo-2-(trifluoromethoxy)benzoyl]azetidine;
2,2,2-Trifluoro-N-methyl-N-(5-methylisoxazol-4-yl)acetamide;

1-[1-Methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]ethanone;
(2E)-3-(Dimethylamino)-1-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]prop-2-en-1-one;
(2Z)-3-(Dimethylamino)-2-fluoro-1-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]prop-2-en-1-one;
5-Fluoro-4-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine;
4-[4-Bromo-2-(methylsulfonyl)benzyl]morpholine;
2-[(4-Bromophenyl)sulfonyl]ethyl methyl ether;
2-[(4-Bromophenyl)sulfonyl]ethyl diethyl-amine;
N-(5-Methyl-isoxazol-4-yl)-N-(tetrahydro-pyran-4-yl)-formamide;
5-Acetyl-1-(tetrahydro-pyran-4-yl)-1H-imidazole;
(E)-3-Dimethylamino-1-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-propenone;
(Z)-3-Dimethylamino-2-fluoro-1-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-propenone;
5-Fluoro-4-[1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine; and
5-{5-Fluoro-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenylamino]-pyrimidin-4-yl}-1-(tetrahydro-pyran-4-yl)-1H-imidazole-2-carbaldehyde.

The present invention also provides the use of the compounds disclosed above for the preparation of a compound of formula **I**.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

In this specification the term "alkyl" includes both straight and branched chain as well as cyclic alkyl groups. The term C_{1-3}alkyl having 1 to 3 carbon atoms and may be, but is not limited to, methyl, ethyl, *n*-propyl, *i*-propyl, or cyclopropyl. The term C_{1-6}alkyl having 1 to 6 carbon atoms and may be, but is not limited to, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, *i*-pentyl, *t*-pentyl, *neo*-pentyl, *n*-hexyl, *i*-hexyl or cyclohexyl. The term C_6alkyl having 6 carbon atoms and may be, but is not limited to, *n*-hexyl, *i*-hexyl or cyclohexyl. The term C_{1-4}alkylNR^bR^c includes, but is not limited to, -$CH_2NR^bR^c$, -$CH_2CH_2NR^bR^c$ and -$CH(CH_3)NR^bR^c$. The term C_{0-2}alkyl$C(O)NR^bR^c$ is

intended to include, but is not limiting, $C(O)NR^bR^c$ $-CH_2C(O)NR^bR^c$, $-CH_2CH_2C(O)NR^bR^c$ and $-CH(CH_3)C(O)NR^bR^c$.

The term "alkenyl" refers to a straight or branched chain alkenyl group. The term C_6alkenyl having 6 carbon atoms and one double bond, and may be, but is not limited to, hexenyl or *i*-hexenyl.

The term "alkynyl" refers to a straight or branched chain alkynyl group. The term C_6alkynyl having 6 carbon atoms and one triple bond, and may be, but is not limited to, hexynyl or *i*-hexynyl.

The term "C_{1-3}alkoxy" includes both straight and branched chains . The term "C_{1-3}alkoxy" having 1 to 3 carbon atoms and may be, but is not limited to, methoxy, ethoxy, n-propoxy, or i-propoxy.

The term "halogen" refers to fluorine, chlorine, bromine and iodine.

The term "haloalkyl" refers to an alkyl group, defined as above, in which one or more of the hydrogen substituents have been replaced by halogen substituents, in which the term halogen is defined as above. Examples include trifluoromethyl- and difluoromethyl-.

The term "aryl" refers to an optionally substituted monocyclic or bicyclic hydrocarbon ring system containing at least one unsaturated aromatic ring. The "aryl" may be fused with a C_{5-7}cycloalkyl ring to form a bicyclic hydrocarbon ring system. Examples and suitable values of the term "aryl", but not limiting,are phenyl, naphthyl, indanyl or tetralinyl.

As used herein, "heteroaryl" refers to an aromatic heterocycle having at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl (i.e., pyridinyl), pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl (i.e. furanyl), quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl,

isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, fluorenonyl, benzimidazolyl, indolinyl, and the like. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 4 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl or heteroaromatic group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms. In some embodiments, the heteroaryl or heteroaromatic group has 1 heteroatom.

The term "heterocyclic ring" refers to a 4-, 5-, 6- or 7-membered ring containing one or more heteroatoms independently selected from N, O, or S, said ring can be a mono- or bicyclic, which may be saturated or partly saturated and which may optionally contain a carbonyl function and which may be, but is not limited to, azetidinyl, imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidinyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, 1-methyl-1,4-diazepane, tetrahydropyranyl or thiomorpholinyl. In the case where the heterocyclic ring contains a heteroatom selected from S or N, these atoms may optionally be in an oxidised form, such as S this includes optionally SO and SO_2.

The term "hydrochloride" includes monohydrochloride, dihydrochloride, trihydrochloride and tetrahydrochloride salts.

A suitable pharmaceutically acceptable salt of the compound of the invention is, for example, an acid-addition salt, for example an inorganic or organic acid. In addition a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base that affords a physiologically-acceptable cation.

Some compounds of formula **I** may have stereogenic centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers.

The present invention relates to the use of compounds of formula **I** as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula **I**.

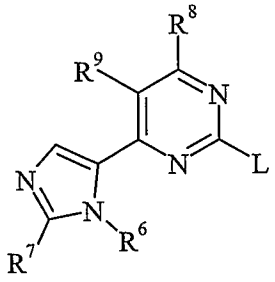
It is to be understood that the present invention relates to any and all tautomeric forms of the compounds of formula **I**.

An object of the invention is to provide compounds of formula **I** for therapeutic use, especially compounds that are useful for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 (GSK3) in mammals including man. Particularly, compounds of formula **I** exhibiting a selective affinity for GSK-3.

Methods of Preparation

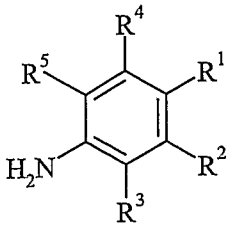
Another aspect of the present invention provides a process for preparing a compound of formula **I**, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, which process (wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 and are, unless otherwise specified, as defined in formula **I**) comprises of:

Process a) reaction of a pyrimidine of formula **(II)**:



(II)

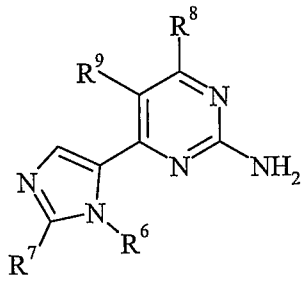
wherein L is a displaceable group; with an aniline of formula **(III)**:



(III)

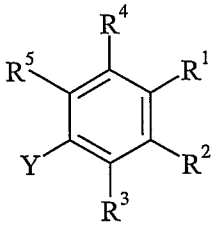
or

Process b) reacting a pyrimidine of formula **(IV)**:



(IV)

with a compound of formula **(V)**:



(V)

wherein Y is a displaceable group;

and thereafter if necessary:

i) converting a compound of the formula **I** into another compound of the formula **I**;

ii) removing any protecting groups; and

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

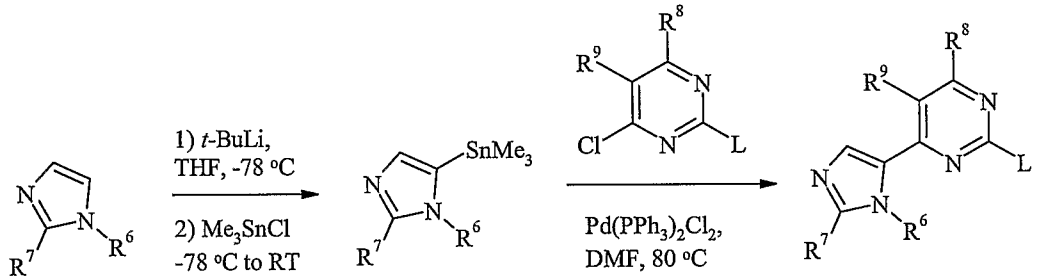
L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

Y is a displaceable group, suitable values for Y are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, iodo or trifluoromethanesulphonyloxy group. Preferably Y is bromo or iodo.

Specific reaction conditions for the above reactions are as follows.

Process a). Pyrimidines of formula **(II)** and anilines of formula **(III)** may be reacted together under standard Buchwald-Hartwig conditions (for example see *J. Am. Chem. Soc.*, **118**, 7215; *J. Am. Chem. Soc.*, **119**, 8451; *J. Am. Chem. Soc.*, **125**, 6653; *J. Org. Chem.*, **62**, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-*t*-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or 2-dicyclohexylphosphino-2',4',6'-triiso-propyl-1,1'-biphenyl and at a temperature in the range of +25 to +80°C.

Pyrimidines of the formula **(II)**, in which R^6 is CH_3 and L is chloro, may be prepared according to *Scheme 1*:



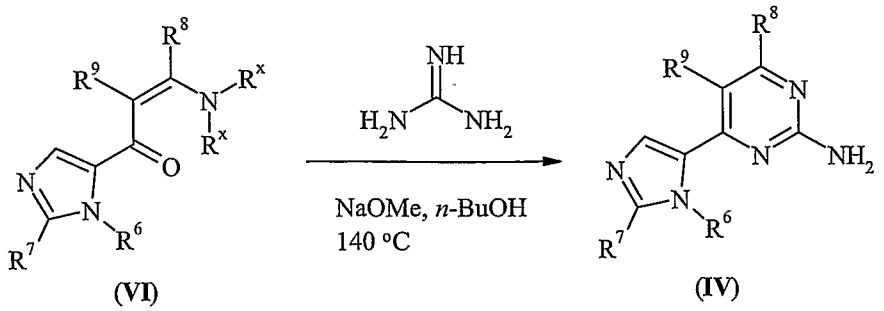
(II)

Scheme 1

Anilines of formula **(III)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process b). Compounds of formula **(IV)** and amines of formula **(V)** may be reacted together under standard Buchwald conditions as described in *Process a*.

A synthesis of pyrimidines of formula **(IV)** is described in *Scheme 2*(R^x may be the same or different and is C_{1-6}alkyl):T should not be there

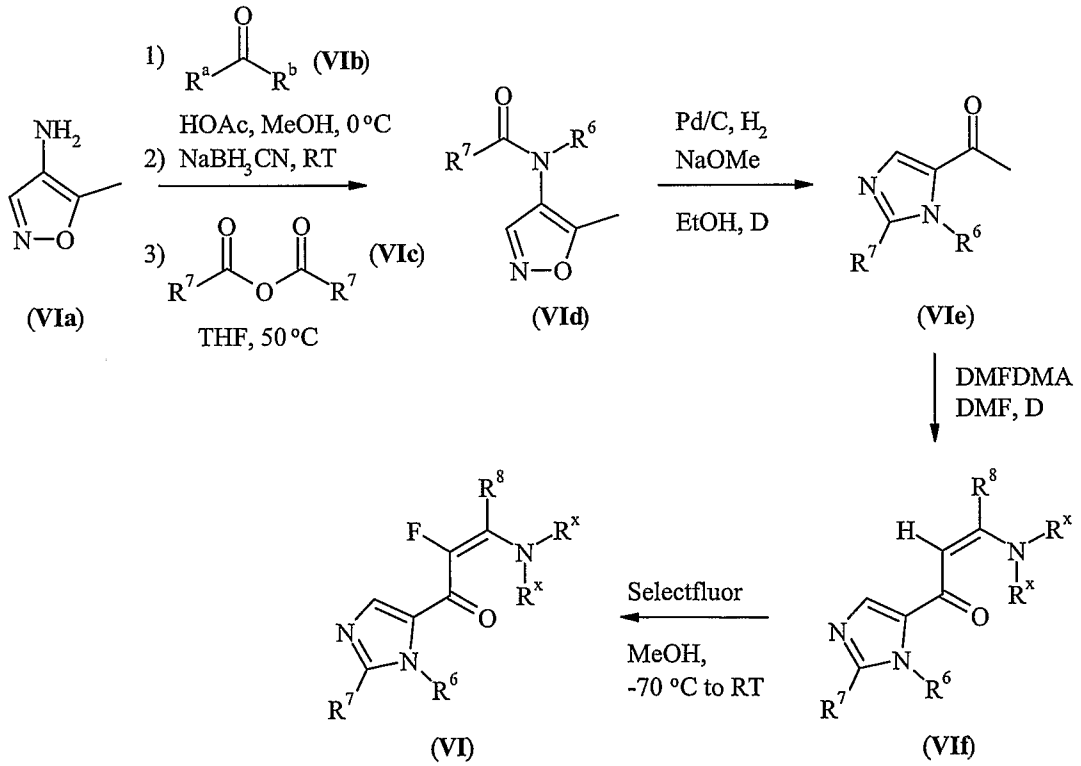


(VI) (IV)

Scheme 2

Compounds of formula **(V)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Compounds of formula **(VI)** in which R^6 has the general structure R^a-CH-R^b (wherein R^a and R^b are as defined in formula I and R^x may be the same or different and is C_{1-6}alkyl) and R^9 is F may be prepared according to *Scheme 3*



Scheme 3

Compounds of formula **(VIa)**, **(VIb)** and **(VIc)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

In one aspect of the invention, there is provided a process for preparing a compound of formula **I** which is a process selected from *Process a)* and *Process b)*.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1999). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an

arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

The present invention also relates to intermediates for the end products of the present invention. These intermediates are useful in the preparation of a compound of formula I as defined above. These intermediates are represented by, but not limited to, the following

2-Chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine;

2-Methyl-4-[(4-methylpiperazin-1-yl)carbonyl]aniline;

4-[(4-Methylpiperazin-1-yl)carbonyl]-3-nitroaniline;

4-[(4-Methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)aniline;

4-[*N*-Acetyl-*N*-(tetrahydro-2*H*-pyran-4-yl)]amino-5-methylisoxazole;

5-Acetyl-2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazole;

(2*E*)-3-Dimethylamino-1-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;

(2*Z*)-3-Dimethylamino-2-fluoro-1-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;

1-(4-Chloro-2-methoxybenzoyl)-4-methylpiperazine;

1-[4-Bromo-2-(methylsulfonyl)benzoyl]-4-methylpiperazine;

4-(*N*-Acetyl-*N*-cyclohexyl)amino-5-methylisoxazole;

5-Acetyl-1-cyclohexyl-2-methyl-1*H*-imidazole;

(2*E*)-3-Dimethylamino-1-(1-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one;

(2*Z*)-3-Dimethylamino-2-fluoro-1-(1-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one;

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

5-Acetyl-2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazole;

(2*E*)-3-Dimethylamino-1-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;

(2*Z*)-3-Dimethylamino-2-fluoro-1-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

1-(tert-Butoxycarbonyl)-4-(4-bromo-benzenesulfonyl)-piperazine;
5-Acetyl-1-(tetrahydro-2*H*-pyran-4-yl)- 2-trifluoromethyl-1*H*-imidazole;
(2*E*)-3-Dimethylamino-1-[1-(tetrahydro-2*H*-pyran-4-yl)-2-trifluoromethyl-1*H*-imidazol-5-yl]prop-2-en-1-one;
(2*Z*)-3-Dimethylamino-2-fluoro-1-[1-(tetrahydro-2*H*-pyran-4-yl)-2-trifluoromethyl-1*H*-imidazol-5-yl]prop-2-en-1-one;
5-Fluoro-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;
4-[2-Methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;
1-[(4-Bromo-2-chlorophenyl)sulfonyl]-4-methylpiperazine;
(3*R*)-4-[(4-Bromophenyl)sulfonyl]-3-methylmorpholine;
(1*S*,4*S*)-2-[(4-Bromophenyl)sulfonyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane;
Methyl 4-bromo-2-(trifluoromethoxy)benzoate;
4-Bromo-2-(trifluoromethoxy)benzoic acid;
4-Bromo-2-(trifluoromethoxy)benzoic acid;
4-(4-Chloro-2-methylbenzyl)morpholine;
Lithium 4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzoate;
1-(4-Bromo-2-methylbenzoyl)azetidine;
4-Bromo-2-(trifluoromethoxy)benzoic acid;
1-[4-Bromo-2-(trifluoromethoxy)benzoyl]azetidine;
2,2,2-Trifluoro-N-methyl-N-(5-methylisoxazol-4-yl)acetamide;
1-[1-Methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]ethanone;
(2E)-3-(Dimethylamino)-1-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]prop-2-en-1-one;
(2Z)-3-(Dimethylamino)-2-fluoro-1-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]prop-2-en-1-one;
5-Fluoro-4-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine;
4-[4-Bromo-2-(methylsulfonyl)benzyl]morpholine;
2-[(4-Bromophenyl)sulfonyl]ethyl methyl ether;
2-[(4-Bromophenyl)sulfonyl]ethyl diethyl-amine;
N-(5-Methyl-isoxazol-4-yl)-N-(tetrahydro-pyran-4-yl)-formamide;

5-Acetyl-1-(tetrahydro-pyran-4-yl)-1H-imidazole;

(E)-3-Dimethylamino-1-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-propenone;

(Z)-3-Dimethylamino-2-fluoro-1-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-propenone;

5-Fluoro-4-[1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine; and

5-{5-Fluoro-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenylamino]-pyrimid in-4-yl}-1-(tetrahydro-pyran-4-yl)-1H-imidazole-2-carbaldehyde.

General Methods

All solvents used were analytical grade and commercially available anhydrous solvents were routinely used for reactions. Reactions were typically run under an inert atmosphere of nitrogen or argon.

^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Varian Unity+ 400 NMR Spectrometer equipped with a 5mm BBO probehead with Z-gradients, or a Varian Gemini 300 NMR spectrometer equipped with a 5mm BBI probehead, or a Bruker Avance 400 NMR spectrometer equipped with a 60 µl dual inverse flow probehead with Z-gradients, or a Bruker DPX400 NMR spectrometer equipped with a 4-nucleus probehead equipped with Z-gradients, or a Bruker Avance 600 NMR spectrometer equipped with a 5mm BBI probehead with Z-gradients. Unless specifically noted in the examples, spectra were recorded at 400 MHz for proton, 376 MHz for fluorine-19 and 100 MHz for carbon-13. The following reference signals were used: the middle line of DMSO-d_6 δ 2.50 (1H), δ 39.51 (13C); the middle line of CD_3OD δ 3.31 (1H) or δ 49.15 (13C); $CDCl_3$ δ 7.26 (1H) and the middle line of $CDCl_3$ δ 77.16 (13C) (unless otherwise indicated).

Mass spectra were recorded on a Waters LCMS consisting of an Alliance 2795 (LC), Waters PDA 2996 and a ZQ single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ESI) operated in a positive or negative ion mode. The capillary voltage was 3 kV and cone voltage was 30 V. The mass spectrometer was scanned between *m/z* 100-700 with a scan time of 0.3s. Separations were performed on either Waters X-Terra MS C8 (3.5 µm, 50 or 100 mm x 2.1 mm i.d.) or an ACE 3 AQ (100 mm x 2.1 mm i.d.) obtained from ScantecLab. Flow rates were regulated to 1.0 or 0.3 mL/min, respectively. The column temperature was set to +40 °C. A linear gradient was applied using a neutral or acidic mobile phase system, starting at 100% A (A: 95:5 10 mM NH_4OAc:MeCN, or 95:5 8 mM HCOOH:MeCN) ending at 100% B (MeCN).

Alternatively, mass spectra were recorded on a Waters LCMS consisting of an Alliance 2690 Separations Module, Waters 2487 Dual 1 Absorbance Detector (220 and 254 nm) and a Waters ZQ single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ESI) operated in a positive or negative ion mode. The

capillary voltage was 3 kV and cone voltage was 30 V. The mass spectrometer was scanned between *m/z* 97-800 with a scan time of 0.3 or 0.8 s. Separations were performed on a Chromolith Performance RP-18e (100 x 4.6 mm). A linear gradient was applied starting at 95% A (A: 0.1% HCOOH (aq.)) ending at 100% B (MeCN) in 5 minutes. Flow rate: 2.0 mL/min.

Alternatively, compound identification was performed on a GC-MS system (GC 6890, 5973N MSD) supplied by Agilent Technologies. The column used was a VF-5 MS, ID 0.25 mm x 15m, 0.25 µm (Varian Inc.). A linear temperature gradient was applied starting at 40 °C (hold 1 min) and ending at +300 °C (hold 1 min), +25 °C/minute. The mass spectrometer was equipped with a chemial ionisation (CI) ion source and the reactant gas was methane. The mass spectrometer was equipped with an electron impact (EI) ion source and the electron voltage was set to 70 eV. The mass spectrometer scanned between *m/z* 50-500 and the scan speed was set to 3.25 scan/s.

Microwave heating was performed in a single-mode microwave cavity producing continuous irradiation at 2450 MHz.

HPLC analyses were performed on an Agilent HP1000 system consisting of G1379A Micro Vacuum Degasser, G1312A Binary Pump, G1367A Well plate auto-sampler, G1316A Thermostatted Column Compartment and G1315B Diode Array Detector. Column: X-Terra MS, Waters, 3.0 x 100 mm, 3.5 µm. The column temperature was set to +40 °C and the flow rate to 1.0 ml/min. The Diode Array Detector was scanned from 210-300 nm, step and peak width were set to 2 nm and 0.05 min, respectively. A linear gradient was applied, starting at 100 % A (A: 95:5 10 mM NH_4OAc:MeCN) and ending at 100% B (B: MeCN), in 4 min.

Alternatively, HPLC analyses were performed on a Gynkotek P580 HPG consisting of gradient pump with a Gynkotek UVD 170S UV-vis.-detector equipped with a Chromolith Performance RP column (C18, 100 mm x 4.6 mm). The column temperature was set to +25 °C. A linear gradient was applied using MeCN/0.1 trifluoroacetic acid in MilliQ water, run from 10% to 100% MeCN in 5 minutes. Flow rate: 3 ml/min.

A typical workup procedure after a reaction consisted of extraction of the product with a solvent such as ethyl acetate, washing with water followed by drying of the organic phase over $MgSO_4$ or Na_2SO_4, filtration and concentration of the solution *in vacuo*.

Thin layer chromatography (TLC) was performed on Merck TLC-plates (Silica gel 60 F_{254}) and UV visualized the spots. Flash chromatography was performed on a Combi Flash® Companion™ using RediSep™ normal-phase flash columns or using Merck Silica gel 60 (0.040-0.063 mm). Typical solvents used for flash chromatography were mixtures of chloroform/methanol, dichloromethane/methanol, heptane/ethyl acetate, chloroform/methanol/ammonia (aq.) and dichlorormethane/methanol/ NH_3 (aq.). SCX ion exchange columns were performed on Isolute® columns. Chromatography through ion exchange columns were typically performed in solvents such a methanol.

Preparative chromatography was run on a Waters autopurification HPLC with a diode array detector. Column: XTerra MS C8, 19 x 300 mm, 10 µm. Narrow gradients with MeCN/(95:5 0.1M NH_4OAc:MeCN) were used at a flow rate of 20 ml/min. Alternatively, purification was achieved on a semi preparative Shimadzu LC-8A HPLC with a Shimadzu SPD-10A UV-vis.-detector equipped with a Waters Symmetry® column (C18, 5 µm, 100 mm x 19 mm). Narrow gradients with MeCN/0.1% trifluoroacetic acid in MilliQ Water were used at a flow rate of 10 ml/min.

The formation of hydrochloride salts of the final products were typically performed in solvents or solvents mixtures such as diethyl ether, tetrahydrofuran, dichloromethane/toluene, dichloromethane/methanol, followed by addition of 1M hydrogen chloride in diethyl ether.

The following abbreviations have been used:

aq.	aqueous;
$CHCl_3$.	chloroform;
$CDCl_3$	deuterated chloroform;
CD_3OH	deuterated methanol;

CH_2Cl_2	dichloromethane;
Cs_2CO_3	caesium carbonate;
DCM	dichloromethane;
DIPEA	*N, N*-diisopropylethylamine;
DMF	*N-N*-dimethylformamide;
DMFDMA	dimethylformamide dimethylacetal;
DMSO	dimethyl sulphoxide;
DMSO-d_6	deuterated dimethyl sulphoxide;
dppp	1,3-bis(diphenylphosphino)propane;
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide;
ether	diethyl ether;
EtOAc	ethyl acetate;
EtOH	ethanol;
H_2	hydrogen gas;
HCOOH	acetic acid;
HCl	hydrochloride;
HOAc	acetic acid;
HOBt	1-hydroxybenzotriazole;
$(i\text{-}Pr)_2NEt$	*N-N*-diisopropylethylamine;
MeCN	acetonitrile;
MeI	methyl iodide;
CD_3OD	deuterated methanol;
MeOH	methanol;
Me_3SnCl	trimethyltin chloride;
$MgSO_4$	magnesium sulphate;
$NaBH_3CN$	sodium cyanoborohydride;
$NaHCO_3$	sodium bicarbonate;
NaOMe	sodium methoxide;
Na_2SO_4	sodium sulphate;
n-BuOH	n-butanol;
NH_3	ammonia;
NH_4OAc	ammonium acetate;

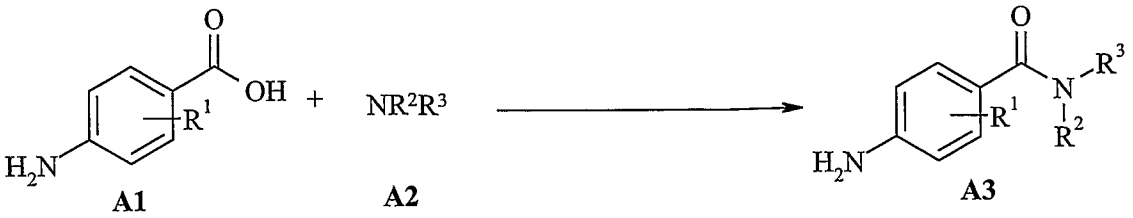
NH_4OH	ammonium hydroxide;
Pd/C	palladium on carbon;
$Pd(PPh_3)_2Cl_2$	bis(triphenylphosphine)palladium dichloride;
$Pd(t\text{-}Bu_3P)_2$	bis(tri-tert-butylphosphine)palladium;
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium;
$Pd(OAc)_2$	palladium diacetate;
r.t. or RT	room temperature;
Selectfluor	*N*-fluoro-*N'*-chloromethyl-triethylenediamine-bis(tetrafluoroborate);
t-BuLi	tert-butyllithium;
THF	tetrahydrofuran;
X-Phos	2-dicyclohexylphosphino-2',4',6'-triiso-propyl-1,1'-biphenyl.

Starting materials used were either available from commercial sources or prepared according to literature procedures and had experimental data in accordance with those reported. The following is an example of a starting material that was prepared: (4-Bromophenyl)(pyridin-2-yl)methanone: Bruce, R.B. et al., *J. Med. Chem.* 1968, *5*, 1031-1034.

Compounds have been named either using ACD/Name, version 8.08, software from Advanced Chemistry Development, Inc. (ACD/Labs), Toronto ON, Canada, www.acdlabs.com, 2004 or using Openeye lexichem version 1.4 (Copyright © 1997-2006 OpenEye Scientific Software, Santa Fe, New Mexico) to generate the IUPAC name.

In the following general methods A to I, the groups R^1, R^2, R^3 and R^4 are used independantly to indicate the diversity of substitution within each structure. The identity of R^1, R^2, R^3 and R^4 will be clear to a person skilled in the art based on the starting materials and intermediates for each specific example. For instance in Example 39, which refers to General method E, E1 is 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine such that R^1 is tetrahydropyranyl, R^3 is methyl and R^4 is hydrogen and E2 is 1-bromo-4-(methylsulfonyl)benzene such that R^2 is sulphonylmethane *para* to the halogen.

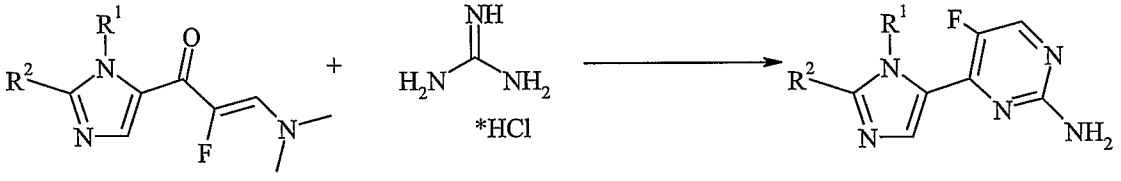
General Method A



A1 **A2** **A3**

(i-Pr)$_2$NEt (2.1 equiv.), HOBt (1.05 equiv.), EDC hydrochloride (1.05 equiv.) and the amine A2 (1.05 equiv.) were added to a stirred solution of the benzoic acid A1 (1.0 equiv.) in anhydrous DMF at r.t.. After 15 h, the reaction mixture was poured onto water and extracted with EtOAc. The organic layer was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to afford the crude product, which was used in the next step without further purification.

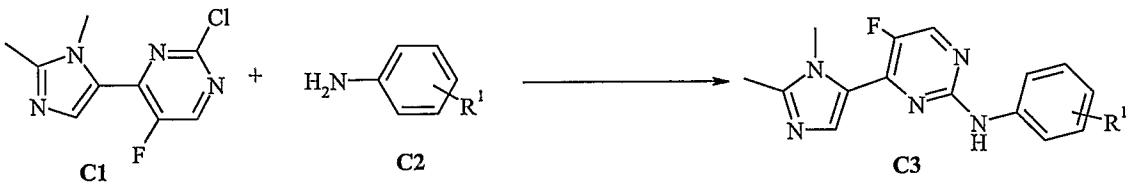
General Method B



B1 **B2** **B3**

A reaction mixture of B1 (1.0 equiv.), guanidine hydrochloride B2 (4.0 equiv.) and sodium methoxide (4.0 equiv.) in 1-butanol was heated in a microwave reactor for 10 minutes at +140 °C under argon or nitrogen atmosphere. The mixture was filtered and the filter was rinsed with CH_2Cl_2. The solvent was evaporated *in vacuo* and the crude product was purified using flash column chromatography.

General Method C



C1 **C2** **C3**

2-Chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine C1 (1.0 equiv.), aniline C2 (1.1 equiv.) and sodium tert-butoxide (1.4 equiv.) were mixed in 1,4-dioxane and the mixture was flushed with argon for 5 minutes. $Pd(OAc)_2$ (0.05 equiv.) and Pd(t-$Bu_3P)_2$

(0.05 equiv.) were added and the reaction was stirred for 15 h at +110 °C. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and water. After extraction the organic layer was dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford a crude material which was purified by preparative HPLC.

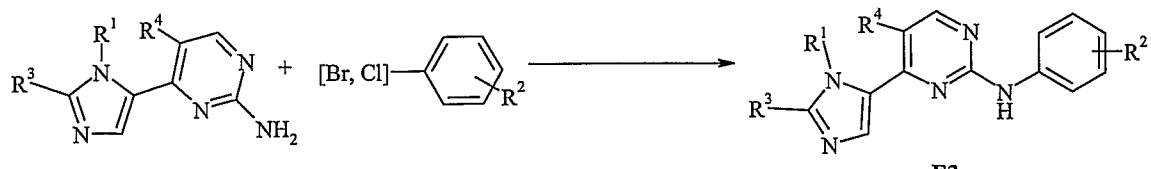
General Method D



D1 **D2** **D3**

D1 (1.0 equiv.), **D2** (0.85-1.24 equiv.) and sodium tert-butoxide (1.34-1.46 equiv.) were mixed in 1,4-dioxane and the mixture was flushed with argon for 5-10 minutes before $Pd(OAc)_2$ (0.04-0.082 equiv.) and $Pd(t\text{-}Bu_3P)_2$ (0.044-0.06 equiv.) were added. The mixture was flushed with argon then heated in a sealed tube at +110-+120 °C until the reaction was complete (as monitored by TLC or LC-MS). If the reaction was not complete after 24 h more $Pd(OAc)_2$, $Pd(t\text{-}Bu_3P)_2$ and sodium tert-butoxide were added. The solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water. After extraction the organic layer was dried (Na_2SO_4), filtered and evaporated. The crude of the free base was purified using preparative HPLC. MeCN was evaporated *in vacuo* and the aqueous phase was extracted with CH_2Cl_2. The organic phase was washed with water at pH 9 (diluted $NaHCO_3$ solution), dried (Na_2SO_4), filtered and evaporated. The residue was dissolved in CH_2Cl_2 and the HCl-adduct of the product was precipitated from the solution by addition of 0.1M HCl in ether (1-5 equiv. HCl). The solvent was evaporated and the residue was dissolved in water and freeze dried.

General Method E



E1 **E2** **E3**

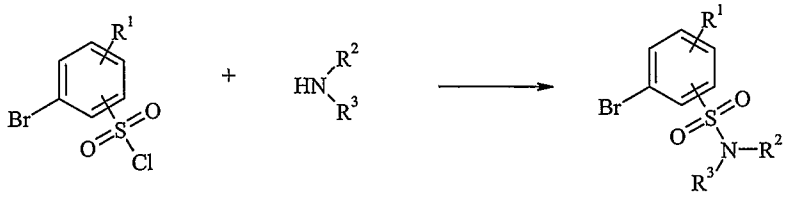
E1 (0.85-1.27 equiv.), **E2** (1.0 equiv.) and Cs_2CO_3 (1.29-2.25 equiv.) were mixed in anhydrous 1,4-dioxane and the mixture was flushed with argon for 5-10 minutes before

$Pd_2(dba)_3$ (0.02-0.08 equiv.) and X-Phos (0.04-0.16 equiv.) were added. The mixture was flushed with argon, then heated in a sealed tube at +90-+100 °C until the reaction was complete.

Workup and purification was performed according to either procedure A, B or C as follows. *Procedure A)* The solvent was removed *in vacuo* and the residue was taken up in CH_2Cl_2 and washed with diluted $NaHCO_3$ (aq.) or water. The organic layer was dried (Na_2SO_4), filtered and evaporated. The crude of the base product was purified using preparative HPLC. *Procedure B)* The reaction mixture was diluted with H_2O or a mixture of $H_2O/CHCl_3$, the product was extracted with $CHCl_3$, the combined organic phases was, if needed, dried (Na_2SO_4), filtered, concentrated and purified using flash column chromatography. *Procedure C)* The reaction mixture was diluted with CH_2Cl_2, filtered and evaporated. The residue was taken up in CH_2Cl_2 and the organic phase was washed with H_2O. Residual water was removed from the organic phase either by treatment with Na_2SO_4 or addition of absolute EtOH before evaporation. The crude of the base product was purified using preparative HPLC.

Alternatively, the general example above was followed but with a slight modification in the order of addition of reagents. For example Cs_2CO_3 can be added together with E1 and E2 before the first argon flush.

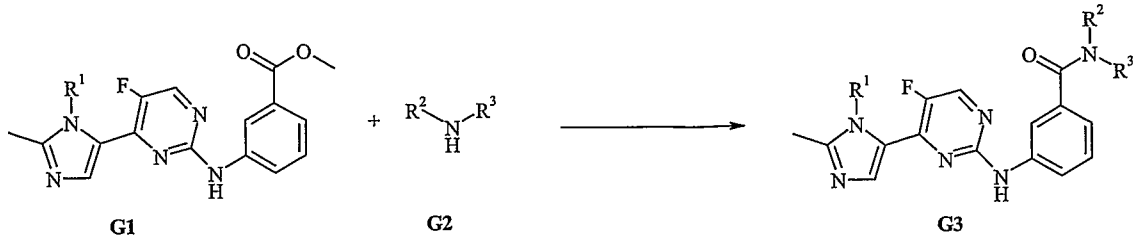
General Method F



F1 **F2** **F3**

F1 (1 equiv) was dissolved in CH_2Cl_2 (2 mL) and **F2** (1.0-1.1 equiv) was added. The reaction mixture was stirred at room temperature for 3 hours whereafter it was washed with saturated $NaHCO_3$ (2 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated to afford **F3**.

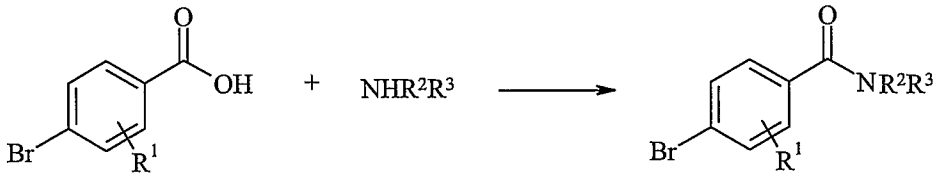
General Method G



G1 G2 G3

G1 (1.0 equiv.) and **G2** (6.0 equiv.) was mixed in toluene (1 - 4 mL) in a thick walled vial of ~10 mL volume and an inert atmospere (Ar or N_2) was established. The sealed vial was cooled in an oil bath (r.t.) or in a dry-ice / ethanol bath (-70°C) and $Al(CH_3)_3$, (2M in toluene) (10 equiv.) was added by a syringe. The reaction mixture was heated in an oil-bath at +90-100°C for 1–4 h, cooled to r.t., and added dropwise into ice-cold sat. $NaHCO_3$ (aq) under vigorous stirring. The product was extracted with CH_2Cl_2 and the organic layer was dried, either by treatment with Na_2SO_4 or addition of absolute EtOH before evaporation. The crude base of the product was purified using flash column chromatography or preparative HPLC.

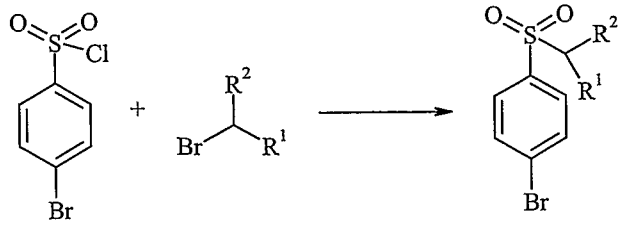
General Method H



H1 H2 H3

Thionyl chloride (5 mL) was added to **H1** (1.0 equiv.). After addition of 2 drops of anhydrous DMF, the reaction mixture was refluxed for 15-30 minutes under an atmosphere of nitrogen. The solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (until a clear solution was obtained). **H2** (1.0 equiv .) was added dropwise followed by addition of triethylamine (1.0 equiv .). The reaction mixture was stirred at r.t. for 15-30 minutes before it was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ (aq.), dried (Na_2SO_4) and filtered. The solvent was evaporated *in vacuo* and the crude product was purified using flash column chromatography.

General Method I



I1 I2 I3

Sulfones of the type **I3** were prepared following a modified procedure from Richard W. Brown (*J. Org. Chem.* **1991**, *56*, 4974-4976). 4-Bromobenzenesulfonyl chloride (**I1**, 1 equiv.), Na_2SO_3 (1 equiv.) and $NaHCO_3$ (3 equiv.) in water (0.2M) were stirred at +90°C for 1 hour. **I2** (1-3 equiv.) was then added and the resulting mixture stirred at +50-100 °C until the formation of the sulfone **I3** was completed according to GC-MS analysis. Water was added to the reaction mixture and extracted with DCM. After extraction the organic layer was dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford a crude material which was purified by flash chromatography.

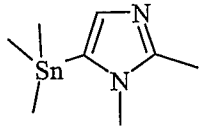
EXAMPLES

Below follows a number of non-limiting examples of compounds of the invention.

Example 1

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[3-methoxy-5-(trifluoromethyl)phenyl]pyrimidin-2-amine

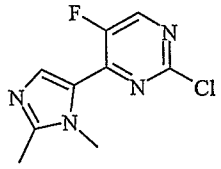
Example 1(a) 1,2-Dimethyl-5-(trimethylstannyl)-1N-imidazole



1,2-Dimethylimidazole (0.960 g, 10.0 mmol) was diluted in dry THF (50 mL) under an argon atmosphere and the solution was cooled to -78°C. tert-Butyllithium (1.7M in pentane, 6.47 mL, 11.0 mmol) was added dropwise over 5 minutes. The reaction mixture was stirred for 1 h at –78 °C and then treated with a solution of trimethyltin chloride (2.2 g, 11.0 mmol) in anhydrous THF (10 mL). The mixture was stirred for 60 h from -78°C to r.t.. The solvent was then evaporated *in vacuo* to give the title compound (1.29 g, 50%). The crude product was used in the next step without further purification.

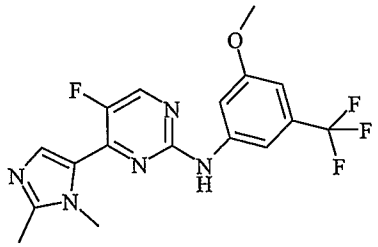
^{1}H NMR ($CDCl_3$) δ ppm 6.87 (s, 1 H), 3.56 (s, 3 H), 2.41 (s, 3 H), 0.45-0.18 (m, 9 H); MS (CI) m/z 261 (^{120}Sn) (M+1).

Example 1(b) 2-Chloro-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidine



1,2-Dimethyl-5-(trimethylstannyl)-1*H*-imidazole (0.950 g, 3.68 mmol, obtained from Example 1(a)) and 2,4-dichloro-5-fluoropyrimidine (0.601 g, 3.60 mmol) were diluted in anhydrous DMF (20 mL) and the solution was degassed with argon. $Pd(PPh_3)_2Cl_2$ (0.126 g, 0.17 mmol) was added and the reaction mixture was stirred at +80 °C for 15 h. The reaction mixture was cooled down to r.t. and concentrated under reduced pressure. Saturated potassium fluoride (aq., 50 mL) was added and the mixture was stirred for 30 minutes before extraction with EtOAc. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (heptane/EtOAc, 7:3) to give the title compound (0.41 g, 50%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ ppm 8.40 (d, *J*=2.9 Hz, 1 H), 7.86 (d, *J*=4.4 Hz, 1 H), 3.97 (s, 3 H), 2.53 (s, 3 H); MS (ESI) m/z 227 (M+1).

Example 1(c) 4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoro-N-[3-methoxy-5-(trifluoromethyl)phenyl]pyrimidin-2-amine

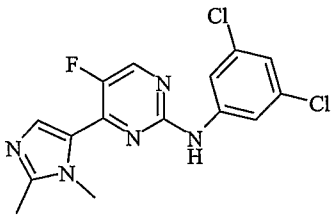


The title compound was prepared in accordance with the general method C using 2-chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (50 mg, 0.221 mmol, obtained from Example 1(b)) and 3-methoxy-5-(trifluoromethyl)aniline (46 mg, 0.243 mmol) to give the title compound (21 mg, 25%).

^{1}H NMR ($CDCl_3$) δ ppm 8.39-8.18 (m, 1 H), 7.75 (d, *J*=4.3 Hz, 1 H), 7.46 (s, 1 H), 7.30 (s, 1 H), 7.14 (s, 1 H), 6.81 (s, 1 H), 4.00-3.89 (m, 3 H), 3.85 (s, 3 H), 2.49 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -63.16 (s, 3 F), -144.69 (t, 1 F); MS (ESI) m/z 382 (M+1).

Example 2

***N*-(3,5-Dichlorophenyl)-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine**

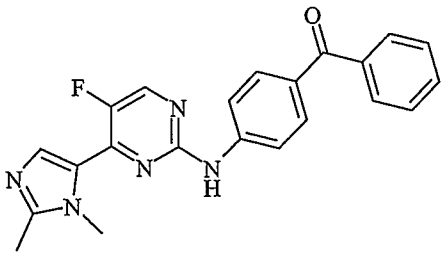


The title compound was prepared in accordance with the general method C using 2-chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (obtained from Example 1(b)) (50 mg, 0.221 mmol) and 3,5-dichloroaniline (39 mg, 0.243 mmol) to give the title compound (15 mg, 19%).

^{1}H NMR (DMSO-d_6) δ ppm 10.12 (s, 1 H), 8.74 (d, *J*=2.8 Hz, 1 H), 7.96 (d, *J*=2.8 Hz, 1 H), 7.79 (d, *J*=2.0 Hz, 1 H), 7.72-7.55 (m, 1 H), 7.16 (t, *J*=1.8 Hz, 1 H), 4.00 (s, 3 H), 2.57 (s, 3 H); MS (ESI) m/z 352 (M+1).

Example 3

(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(phenyl)methanone



The title compound was prepared in accordance with the general method C using 2-chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (obtained from Example 1(b)) (80 mg, 0.354 mmol) and (4-aminophenyl)(phenyl)methanone (84 mg, 0.424 mmol), $Pd(OAc)_2$

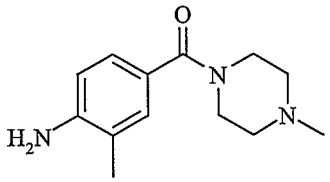
(4.7 mg, 0.021 mmol) and Pd(*t*-$Bu_3P)_2$ (10.7 mg, 0.021 mmol) to give the title compound (56 mg, 41%).

^{1}H NMR ($CDCl_3$) δ ppm 8.32 (s, 1 H), 8.00-7.63 (m, 7 H), 7.60-7.33 (m, 4 H), 3.96 (s, 3 H), 2.51 (s, 3 H); MS (ESI) m/z 388 (M+1).

Example 4

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine

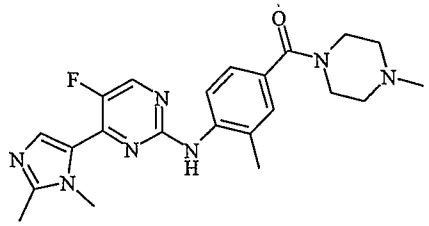
Example 4(a) 2-Methyl-4-[(4-methylpiperazin-1-yl)carbonyl]aniline



The title compound was prepared in accordance with the general method A using *N*-methylpiperazine (0.44 mL, 4.0 mmol) and 4-amino-3-methylbenzoic acid (0.692 g, 3.8 mmol) to give the title compound (0.421 g, 47%).

^{1}H NMR ($CDCl_3$) δ ppm 7.30 (s, 1 H), 7.21 (s, 1 H), 7.18-7.10 (m, 1 H), 4.50-3.80 (br s, 4 H), 3.91 (s, 3 H), 3.20-2.50 (br s, 4 H), 2.77 (m, 7 H).

Example 4(b) 4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoro-N-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine



The title compound was prepared in accordance with the general method C using 2-chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (obtained from Example 1(b)) (50 mg, 0.221 mmol) and 2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]aniline (57 mg, 0.243 mmol) to give the title compound (15 mg, 16%).

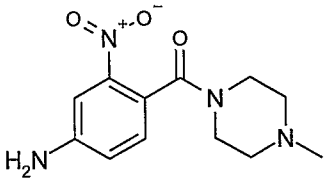
^{1}H NMR (CD_3OD) δ ppm 8.31 (d, *J*=3.5 Hz, 1 H), 7.70 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=4.0 Hz, 1 H), 7.35 (s, 1 H), 7.29 (dd, *J*=8.2, 1.9 Hz, 1 H), 3.83 (s, 3 H), 3.79-3.42 (m, 4 H),

2.63-2.47 (m, 4 H), 2.45 (s, 3 H), 2.38 (s, 3 H), 2.35 (s, 3 H); ^{19}F NMR (CD_3OD) δ ppm -151.35 (s, 1 F); MS (ESI) m/z 424 (M+1).

Example 5

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]-3-nitrophenyl}pyrimidin-2-amine

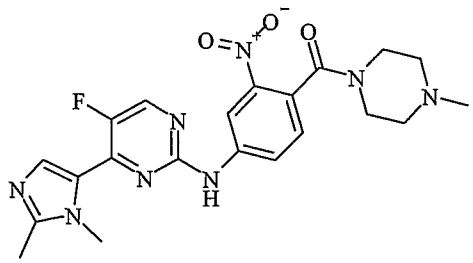
Example 5(a) 4-[(4-Methylpiperazin-1-yl)carbonyl]-3-nitroaniline



The title compound was prepared in accordance with the general method A using *N*-methylpiperazine (0.44 mL, 4.0 mmol) and 4-amino-2-nitrobenzoic acid (0.692 g, 3.8 mmol) to give the title compound (0.531 g, 53%).

^{1}H NMR (CD_3OD) δ ppm 7.39 (d, *J*=2.3 Hz, 1 H), 7.13 (d, *J*=8.1 Hz, 1 H), 6.91 (dd, *J*=8.1, 2.3 Hz, 1 H), 4.16 (s, 2 H), 3.96 (s, 2 H), 3.41 (s, 2 H), 2.69 (s, 2 H), 2.59-2.48 (m, 2 H), 2.47-2.36 (m, 3 H).

Example 5(b) 4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoro-N-{4-[(4-methylpiperazin-1-yl)carbonyl]-3-nitrophenyl}pyrimidin-2-amine



The title compound was prepared in accordance with the general method C using 2-chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (obtained from Example 1(b)) (50 mg, 0.221 mmol) and 4-[(4-methylpiperazin-1-yl)carbonyl]-3-nitroaniline (64 mg, 0.243 mmol, obtained from Example 5(a)) to give the title compound (21 mg, 21%).

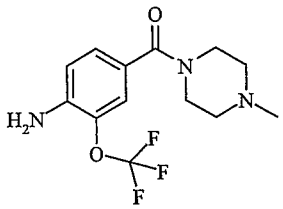
^{1}H NMR (CD_3OD) δ ppm 8.80 (d, *J*=2.0 Hz, 1 H), 8.45 (d, *J*=3.3 Hz, 1 H), 7.97 (dd, *J*=8.3, 2.1 Hz, 1 H), 7.66 (d, *J*=4.0 Hz, 1 H), 7.40 (d, *J*=8.3 Hz, 1 H), 4.06 (s, 3 H), 3.83 (s,

2 H), 3.43-3.36 (m, 2 H), 2.61 (t, *J*=5.2 Hz, 2 H), 2.55-2.48 (s, 3 H), 2.48-2.41 (m, 2 H), 2.37 (s, 3 H); ^{19}F NMR (CD_3OD) δ ppm -147.52 (s, 1 F); MS (ESI) m/z 455 (M+1).

Example 6

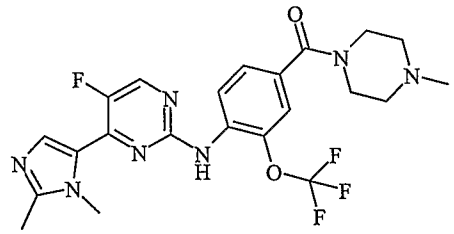
4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-[(4-methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)phenyl]pyrimidin-2-amine hydrochloride

Example 6(a) 4-[(4-Methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)aniline



The title compound was prepared in accordance with the general method A using *N*-methylpiperazine (0.44 mL, 4.0 mmol) and 4-amino-3-(trifluoromethyoxy)benzoic acid (0.840 g, 3.8 mmol) to give the title compound (0.663 g, 57%).
^{1}H NMR (CD_3OD) δ ppm 7.33 (s, 1 H), 7.25 (dd, *J*=8.2, 1.9 Hz, 1 H), 6.83 (d, *J*=8.2 Hz, 1 H), 4.21 (s, 2 H), 3.96 (s, 4 H), 3.16-2.33 (m, 7 H).

Example 6(b) 4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoro-N-[4-[(4-methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)phenyl]pyrimidin-2-amine hydrochloride



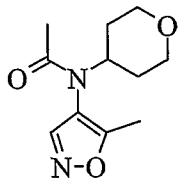
The base of the title compound was prepared in accordance with the general method C using 2-chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (obtained from Example 1(b)) (50 mg, 0.221 mmol) and 4-[(4-methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)aniline (73 mg, 0.243 mmol, obtained from Example 6(a)). The hydrochloride salt was obtained by dissolving the base product in anhydrous THF (5 mL) and a solution of 1M HCl in ether (1 mL) was added. The solvent was evaporated *in vacuo* and the residue was dried to give the title compound (21 mg, 19%).

^{1}H NMR (CD_3OD) δ ppm 8.62 (s, 1 H), 8.23 (s, 1 H), 8.13 (s, 1 H), 7.57 (br s, 2 H), 4.39 (s, 2 H), 4.09 (s, 3 H), 3.57 (s, 4 H), 3.24 (s, 2 H), 2.96 (s, 3 H), 2.76 (s, 3 H); ^{19}F NMR (CD_3OD) δ ppm -59.79 (s, 3 F), -147.62 (s, 1 F); MS (ESI) m/z 494 (M+1).

Example 7

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride

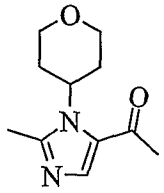
Example 7(a) 4-[N-Acetyl-N-(tetrahydro-2H-pyran-4-yl)]amino-5-methylisoxazole



5-Methyl-4-amino-isoxazole (Reiter, L.A., *J. Org. Chem.* **1987**, *52,* 2714-2726) (0.68 g, 5.1 mmol) and acetic acid (0.61 g, 10.2 mmol) were dissolved in MeOH (20 mL). Tetrahydro-2*H*-pyran-4-one (0.76 g, 7.6 mmol) was added and the mixture was cooled to 0 – (-5) °C and stirred for 1 h. Sodium cyanoborohydride (0.32 g, 5.1 mmol) was added to the reaction mixture at –5 °C, causing weak exothermic and gas evolution. The cooling bath was removed and the mixture was stirred at r.t. for 1 h, followed by the addition of a second portion of sodium cyanoborohydride (0.1 g, 1.6 mmol). After stirring for 2 h at r.t., the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in toluene and re-concentrated. The residue was dissolved in THF (10 mL) and acetic anhydride (1.56 g, 15.3 mmol) was added. The resulting mixture was stirred overnight at r.t. then for 1 h at +50 °C. The volatiles were removed *in vacuo* and the residue was dissolved in toluene and concentrated *in vacuo* to give the title compound (1.36 g, 78%) as a solid.

^{1}H NMR ($CDCl_3$) ppm δ 8.04 (s, 1 H), 4.86–4.73 (m, 1 H), 4.00–3.89 (m, 2 H), 3.52-3.42 (m, 2 H), 2.35 (s, 3 H), 1.81 (s, 3 H), 1.70-1.57 (m, 2 H), 1.49-1.23 (m, 2 H); MS (ESI) *m/z* 225 (M+1).

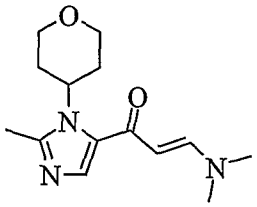
Example 7(b) 5-Acetyl-2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazole



Sodium bicarbonate(0.8 g, 9.52 mmol) was added to a stirred solution of 4-[*N*-acetyl-*N*-(tetrahydro-2*H*-pyran-4-yl)]amino-5-methylisoxazole (4.8 g, 21.4 mmol, obtained from Example 7(a)) in EtOH (30 ml), and the mixture was hydrogenated over Pd/C (10%, wet paste, 0.10 g) at 3 bar. The reaction mixture was stirred at +50 °C for 3 h. An additional amount of Pd/C (10%, wet paste, 0.15 g) was added and the mixture was continued stirring at +50 °C for 3 h. Sodium methoxide (1.70 g, 31.46 mmol) was added and the resulting mixture was heated to reflux for 30 h. Ammonium chloride was added to quench the reaction. The mixture was filtrated through diatomaceous earth and the filtrate was evaporated *in vacuo*. The residue was diluted with saturated sodium bicarbonate (aq.) and extracted with EtOAc, then with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (EtOAc) to give the title compound (3.7 g, 83%) as a yellow solid.

^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1 H), 5.40–5.30 (m, 1 H), 4.13–4.01 (m, 2 H), 3.57-3.44 (m, 2 H), 2.57 (s, 3 H), 2.44 (s, 3 H), 2.43-2.30 (m, 2 H), 1.80-1.72 (m, 2 H).

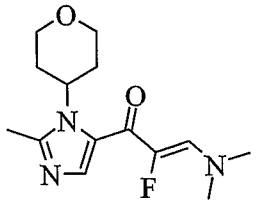
Example 7(c) (2E)-3-Dimethylamino-1-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]prop-2-en-1-one



5-Acetyl-2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazole (3.7 g, 17.79 mmol, obtained 7(b)) was dissolved in DMFDMA/DMF (1:1, 100 mL) and the mixture was stirred under reflux overnight. After cooling to r.t. the mixture was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 15:1) to give the title compound (3.85 g, 82%) as an oil that crystallized in the refrigerator.

^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 12.6 Hz, 1 H), 7.46 (s, 1 H), 5.55–5.42 (m, 2 H), 4.08 (dd, J = 11 Hz, 4.4 Hz, 2 H), 3.52 (t, J = 11 Hz, 2 H), 2.99 (br s, 6 H), 2.56 (s, 3 H), 2.45-2.32 (m, 2 H), 1.80-1.72 (m, 2 H); MS (ESI) *m/z* 264 (M+1).

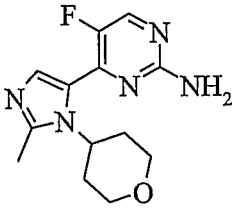
Example 7(d) (2Z)-3-Dimethylamino-2-fluoro-1-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]prop-2-en-1-one



Selectfluor (7.75 g, 21.87 mmol) was added in portions to a stirred solution of (2*E*)-3-dimethylamino-1-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one (3.85 g, 14.58 mmol, obtained from Example 7(c)) in MeOH (100 mL) at r.t. After stirring at r.t. for 3 h the reaction mixture was cooled in ice/acetone and filtered. The filtrate was evaporated under reduced pressure and the residue was taken into CH_2Cl_2. It was washed with aq. ammonia, brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 15:1). The reaction was not run to completion, and the reaction was repeated again with Selectfluor (1.5 equiv.) followed by the same workup. The title compound (1.47 g, 36%) was obtained as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (s, 1 H), 6.84 (d, J = 27.9 Hz, 1 H), 5.00–4.88 (m, 1 H), 4.04 (dd, J = 11.2 Hz, 4.2 Hz, 2 H), 3.46 (t, J = 11 Hz, 2 H), 3.08 (s, 6 H), 2.53 (s, 3 H), 2.42-2.28 (m, 2 H), 1.84-1.75 (m, 2 H); MS (ESI) *m/z* 282 (M^++1).

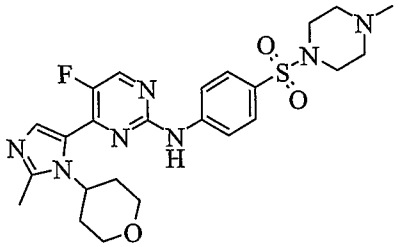
Example 7(e) 5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine



The title compound was prepared in accordance with the general method B with the exception that guanidine carbonate was used. Using (2*Z*)-3-dimethylamino-2-fluoro-1-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]prop-2-en-one (1.47 g, 5.22 mmol, obtained from Example 7(d)) and guanidine carbonate (2.35 g, 13.06 mmol) the title compound (1.21 g, 84%) was obtained as a solid after purification by flash chromatography (CH_2Cl_2/MeOH 20:1).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.17 (d, J = 3.3 Hz, 1 H), 7.59 (d, J = 3.9 Hz, 1 H), 5.27–5.13 (m, 1 H), 4.93 (br s, 2 H), 4.13 (dd, J = 11.5 Hz, 4.3 Hz, 2 H), 3.48 (t, J = 11 Hz, 2 H), 2.62 (s, 3 H), 2.58-2.40 (m, 2 H), 1.95-1.84 (m, 2 H); MS (ESI) *m/z* 278 (M+1).

Example 7(f) 5-Fluoro-N-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride

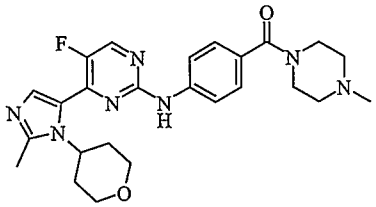


The title compound was prepared in accordance with the general method D, with the exception that the base of the product was purified by flash chromatography ($CHCl_3$/MeOH/NH_3 aq. 200:10:1) before purification by preparative HPLC. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (0.075 g, 0.27 mmol, obtained from Example 7(e)), 1-(4-bromo-benzenesulfonyl)-4-methylpiperazine (described in WO 2003004472) (0.108 g, 0.338 mmol), sodium tert-butoxide (0.036 g, 0.38 mmol), $Pd(OAc)_2$ (0.012 g, 0.054 mmol) and Pd(*t*-$Bu_3P)_2$ (0.14 g, 0.027 mmol), the title compound (0.018 g, 11%) was obtained as a yellow solid.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.64 (br s, 1 H), 10.43 (s, 1 H), 8.90 (s, 1 H), 8.07 (s, 1 H), 7.96 (d, J = 8.4 Hz, 2 H), 7.70 (d, J = 8.4 Hz, 2 H), 5.03–4.93 (m, 1 H), 3.90–3.70 (m, 4 H), 3.36–3.15 (m, 4 H), 2.81 (s, 3 H), 2.74 (s, 3 H), 2.25-2.15 (m, 2 H), 2.00-1.92 (m, 2 H); MS (ESI) *m/z* 516 (M+1).

Example 8

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride



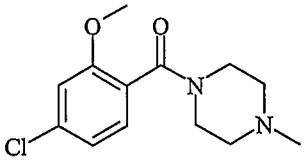
The title compound was prepared in accordance with the general method D, with the exception that the base of the product was purified by flash chromatography ($CHCl_3$/MeOH/NH_3 aq. 200:10:1) before purification by preparative HPLC. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (0.075 g, 0.27 mmol), 1-(4-bromobenzoyl)-4-methylpiperazine (0.115 g, 0.405 mmol), sodium tert-butoxide (0.036 g, 0.38 mmol), $Pd(OAc)_2$ (0.012 g, 0.054 mmol) and $Pd(t\text{-}Bu_3P)_2$ (0.14 g, 0.027 mmol), the base of title compound (0.023 g, 18%) was obtained. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.02 (br s, 1 H), 10.14 (s, 1 H), 8.86 (s, 1 H), 8.12 (s, 1 H), 7.72 (d, J = 8.1 Hz, 2 H), 7.41 (d, J = 8.1 Hz, 2 H), 5.03–4.93 (m, 1 H), 4.25–4.05 (m, 4 H), 3.45–3.35 (m, 4 H), 3.23–3.00 (m, 4 H), 2.83 (s, 3 H), 2.78 (s, 3 H), 2.20-2.10 (m, 2 H), 1.98-1.90 (m, 2 H); MS (ESI) *m/z* 480 (M+1).

Example 9

5-Fluoro-*N*-{3-methoxy-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride

Example 9(a) 1-(4-Chloro-2-methoxybenzoyl)-4-methylpiperazine

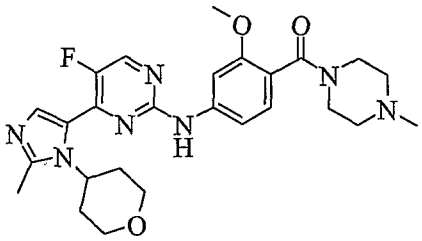


Thionyl chloride (5 mL) was added to 4-chloro-2-methoxybenzoic acid (0.501 g, 2.68 mmol). After addition of 1 drop of anhydrous DMF, the reaction mixture was refluxed for

30 minutes under an atmosphere of nitrogen. The solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (until a clear solution was obtained). *N*-Methylpiperazine (0.31 mL, 2.81 mmol)) was added dropwise followed by addition of triethylamine (0.39 mL, 2.81 mmol). The reaction mixture was stirred at r.t. for 15 minutes before it was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ (aq.), water, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound in quantitative yield. The isolated material was used in the next step without further purification.

^{1}H NMR (DMSO-d_6) δ ppm 7.18 (d, *J*=8.0 Hz, 1 H), 7.17 (d, *J*=2.0 Hz, 1 H), 7.05 (dd, *J*=8.0, 1.8 Hz, 1 H), 3.81 (s, 3 H), 3.67-3.51 (m, 2 H), 3.14-3.04 (m, 2 H), 2.38-2.27 (m, 2 H), 2.27-2.19 (m, 2 H), 2.18 (s, 3 H).

Example 9(b) 5-Fluoro-N-{3-methoxy-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride



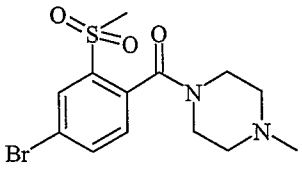
The title compound was prepared in accordance with the general method E, with the exception that the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH/NH_3 aq. 200:10:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (0.075 g, 0.27 mmol), 1-(4-chloro-2-methoxybenzoyl)-4-methylpiperazine (0.065 g, 0.24 mmol, obtained from Example 9(a)), Cs_2CO_3 (176 mg, 0.54 mmol), $Pd_2(dba)_3$ (12 mg, 0.013 mmol) and X-Phos (13 mg, 0.027 mmol), the base of the title compound (105 mg, 67%) was obtained as a white solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.45 (br s, 1 H), 10.08 (s, 1 H), 8.85 (s, 1 H), 8.13 (s, 1 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 7.35 (s, 1 H), 7.18 (d, *J* = 7.8 Hz, 1 H), 5.03–4.93 (m, 1 H), 4.75–4.50 (m, 3 H), 3.90–3.78 (m, 4 H), 3.52–3.39 (m, 4 H), 3.27–3.12 (m, 4 H), 2.85 (s, 3 H), 2.77 (s, 3 H), 2.20-2.10 (m, 2 H), 1.98-1.90 (m, 2 H); MS (ESI) *m/z* 510 (M+1).

Example 10

5-Fluoro-*N*-[4-[(4-methylpiperazin-1-yl)carbonyl]-3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride

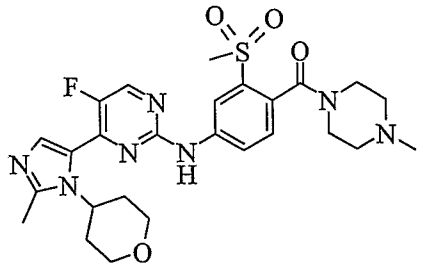
Example 10(a) *1-[4-Bromo-2-(methylsulfonyl)benzoyl]-4-methylpiperazine*



Thionyl chloride (5 mL) was added to 4-bromo-2-(methylsulfonyl)benzoic acid (0.50 g, 1.67 mmol). After addition of 1 drop of anhydrous DMF, the reaction mixture was refluxed for 30 minutes under an atmosphere of nitrogen. The solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (until a clear solution was obtained). *N*-Methylpiperazine (0.195 mL, 1.75 mmol) was added dropwise followed by addition of triethylamine (0.243 mL, 1.75 mmol). The reaction mixture was stirred at r.t. for 15 minutes before it was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ (aq.), water, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound in quantitative yield. The isolated material was used in the next step without further purification.

^{1}H NMR (DMSO-d_6, Signals corresponding to 3 protons were overlapping with the solvents) δ ppm 8.06 (d, *J*=2.0 Hz, 1 H), 8.01 (dd, *J*=8.3, 2.0 Hz, 1 H), 7.46 (d, *J*=8.0 Hz, 1 H), 3.65-3.53 (m, 2 H), 3.19-3.00 (m, 2 H), 2.43-2.33 (m, 2 H), 2.33-2.21 (m, 2 H), 2.19 (s, 3 H); MS (ESI) m/z 361, 363 (M+1).

Example 10(b) *5-Fluoro-N-[4-[(4-methylpiperazin-1-yl)carbonyl]-3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride*

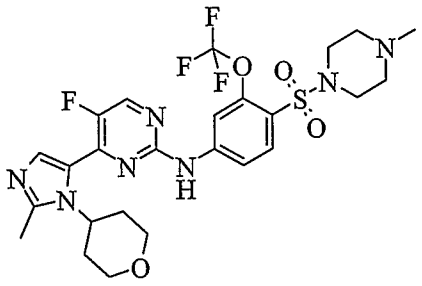


The title compound was prepared in accordance with the general method E, with the exception that the base of the product was purified by flash chromatography ($CHCl_3$/MeOH/NH_3 aq. 200:10:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (67 mg, 0.242 mmol), 1-[4-bromo-2-(methylsulfonyl)benzoyl]-4-methylpiperazine (70 mg, 0.194 mmol, obtained from 10(a)), Cs_2CO_3 (71 mg, 0.22 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol) and X-Phos (10 mg, 0.021 mmol), the base of the title compound (0.100 g, 92%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO- d_6, 300 MHz) δ 11.15 (br s, 1 H), 10.41 (s, 1 H), 8.91 (s, 1 H), 8.30-8.25 (m, 1 H), 8.20-8.11 (m, 2 H), 7.55-7.49 (m, 1 H), 5.01–4.88 (m, 1 H), 4.70–4.50 (m, 1 H), 3.95–3.62 (m, 6 H), 3.59–3.44 (m, 2 H), 3.40–3.08 (m, 7 H), 2.84 (s, 3 H), 2.81-2.75 (m, 3 H), 2.23-2.11 (m, 2 H), 2.01-1.94 (m, 2 H); MS (ESI) *m/z* 558 (M+1).

Example 11

5-Fluoro-*N*-[4-[(4-methylpiperazin-1-yl)sulfonyl]-3-(trifluoromethoxy)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride



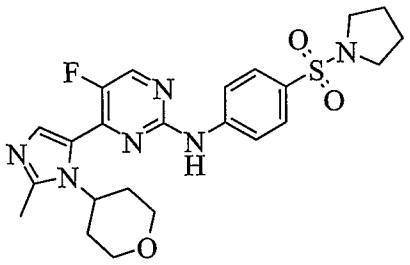
The title compound was prepared in accordance with the general method E, with the exception that the base of the title product was purified by flash chromatography (CH_2Cl_2/MeOH 20:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-

imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (32 mg, 0.116 mmol), 1-(4-bromo-2-trifluoromethoxy-benzenesulfonyl)-4-methyl-piperazine (described in WO 2003004472) (0.042 g, 0.104 mmol), Cs_2CO_3 (38 mg, 0.12 mmol), $Pd_2(dba)_3$ (6 mg, 0.006 mmol) and X-Phos (5 mg, 0.011 mmol), the base of the title compound (38 mg, 61%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6,300 MHz) δ 11.31 (br s, 1 H), 10.70 (s, 1 H), 8.96 (s, 1 H), 8.10 (s, 2 H), 7.96 (d, J = 9.0 Hz, 1 H), 7.84 (d, J = 9.0 Hz, 1 H), 5.00–4.85 (m, 1 H), 3.93–3.83 (m, 2 H), 3.79–3.69 (m, 2 H), 3.48–3.39 (m, 2 H), 3.36–3.25 (m, 2 H), 3.18–2.98 (m, 4 H), 2.84 (s, 3 H), 2.74 (s, 3 H), 2.20-2.10 (m, 2 H), 2.00-1.92 (m, 2 H); MS (ESI) *m/z* 600 (M+1).

Example 12

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride



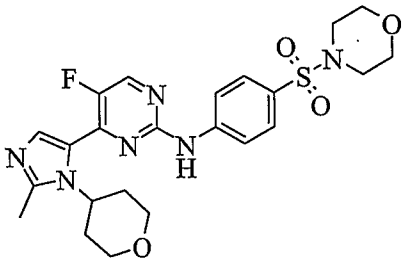
The title compound was prepared in accordance with the general method E, with the exception that the base of the title product was purified by flash chromatography (CH_2Cl_2/MeOH 30:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (35 mg, 0.126 mmol), 1-(4-bromo-benzenesulfonyl)-pyrrolidine (33 mg, 0.113 mmol), Cs_2CO_3 (41 mg, 0.13 mmol), $Pd_2(dba)_3$ (6 mg, 0.007 mmol) and X-Phos (6 mg, 0.012 mmol), the base of the title compound (54 mg, 98%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.37 (s, 1 H), 8.89 (s, 1 H), 8.32 (s, 1 H), 8.10 (s, 1 H), 7.89 (d, J = 8.4 Hz, 2 H), 7.72 (d, J = 8.4 Hz, 2 H), 5.03–4.93 (m, 1 H), 3.87–3.78 (m, 2 H), 3.29–3.07 (m, 6 H), 2.83 (s, 3 H), 2.22-2.12 (m, 2 H), 2.00-1.92 (m, 2 H), 2.64 (s, 4 H);

MS (ESI) *m/z* 487 (M+1).

Example 13

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride

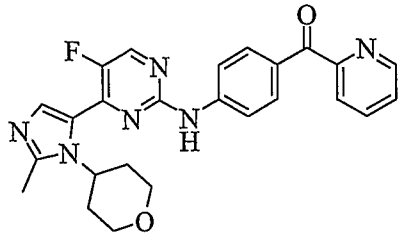


The title compound was prepared in accordance with the general method E, with the exception that the base of the title product was purified by flash chromatography (CH_2Cl_2/MeOH 30:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (30 mg, 0.108 mmol), 4-(4-bromo-benzenesulfonyl)-morpholine (0.032 g, 0.103 mmol), Cs_2CO_3 (38 mg, 0.116 mmol), $Pd_2(dba)_3$ (6 mg, 0.006 mmol) and X-Phos (5 mg, 0.011 mmol), the base of the title compound (52 mg, quantitative yield) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.41 (s, 1 H), 8.90 (s, 1 H), 8.10 (s, 1 H), 7.92 (d, J = 8.4 Hz, 2 H), 7.65 (d, J = 8.4 Hz, 2 H), 5.03–4.91 (m, 1 H), 3.88–3.78 (m, 2 H), 3.62 (s, 4 H), 3.29–3.14 (m, 2 H), 2.85-2.81 (m, 7 H), 2.23-2.12 (m, 2 H), 2.00-1.92 (m, 2 H);
MS (ESI) *m/z* 503 (M+1).

Example 14

[4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)phenyl](pyridin-2-yl)methanone hydrochloride

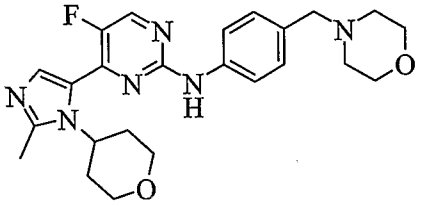


The title compound was prepared in accordance with the general method E, with the exception that the base of the title product was purified by flash chromatography (CH_2Cl_2/MeOH 30:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (35 mg, 0.126 mmol), (4-bromophenyl)(pyridin-2-yl)methanone (Bruce R.B. et al., *J. Med. Chem.* **1968**, *11*, 1031-1034) (32 mg, 0.103 mmol), Cs_2CO_3 (44 mg, 0.13 mmol), $Pd_2(dba)_3$ (6 mg, 0.007 mmol) and X-Phos (6 mg, 0.013 mmol), the base of the title compound (53 mg, 96%) was given as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.40 (s, 1 H), 8.90 (s, 1 H), 8.73-8.68 (m, 1 H), 8.14 (s, 1 H), 8.10-7.89 (m, 4 H), 7.82 (d, J = 8.4 Hz, 2 H), 7.69-7.63 (m, 1 H), 5.07–4.94 (m, 1 H), 3.88–3.80 (m, 2 H), 3.26–3.14 (m, 2 H), 2.85 (s, 3 H), 2.22-2.11 (m, 2 H), 2.01-1.93 (m, 2 H); MS (ESI) *m/z* 459 (M+1).

Example 15

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride

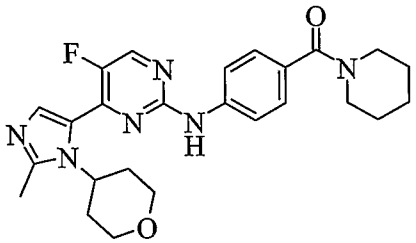


The title compound was prepared in accordance with the general method E, with the exception that the reaction was heated to +100 °C for an additional 20 h, and the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH 15:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (35 mg, 0.126 mmol), 4-(4-bromobenzyl)-morpholine (0.031 g, 0.120 mmol), Cs_2CO_3 (44 mg, 0.13 mmol), $Pd_2(dba)_3$ (6 mg, 0.007 mmol) and X-Phos (6 mg, 0.013 mmol), the base of the title compound (28 mg, 49%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.48 (br s, 1 H), 10.07 (s, 1 H), 8.83 (s, 1 H), 8.09 (s, 1 H), 7.69 (d, J = 8.3 Hz, 2 H), 7.54 (d, J = 8.3 Hz, 2 H), 5.03–4.91 (m, 1 H), 4.25 (s, 2 H), 3.96–3.76 (m, 6 H), 3.25–3.12 (m, 4 H), 3.10–2.97 (m, 2 H), 2.83 (s, 3 H), 2.22-2.11 (m, 2 H), 2.00-1.90 (m, 2 H); MS (ESI) *m/z* 453 (M+1).

Example 16

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-2-amine hydrochloride



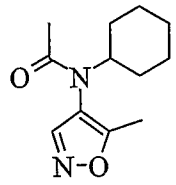
The title compound was prepared in accordance with the general method E, with the exception that the base of the title compound was purified by flash chromatography (CH_2Cl_2/MeOH 25:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (35 mg, 0.126 mmol), 1-(4-bromobenzoyl)piperidine (0.042 g, 0.157 mmol), Cs_2CO_3 (46 mg, 0.14 mmol), $Pd_2(dba)_3$ (7 mg, 0.008 mmol) and X-Phos (7 mg, 0.014 mmol), the base of the title compound (52 mg, 89%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.05 (s, 1 H), 8.83 (s, 1 H), 8.08 (s, 1 H), 7.66 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.4 Hz, 2 H), 5.05–4.94 (m, 1 H), 3.85–3.77 (m, 2 H), 3.50-3.32 (m, 4 H), 3.21–3.09 (m, 2 H), 2.82 (s, 3 H), 2.19-2.10 (m, 2 H), 1.96-1.88 (m, 2 H), 1.63-1.58 (m, 2 H), 1.54-1.42 (m, 4 H); MS (ESI) *m/z* 465 (M+1).

Example 17

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride

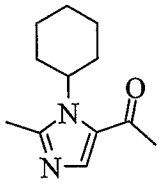
Example 17(a) *4-(N-Acetyl-N-cyclohexyl)amino-5-methylisoxazole*



The title compound was prepared in accordance with the general method of Example 7 (a), with the exception that the product was purified by flash chromatography (heptane/EtOAc 1:1). Using 5-methyl-4-amino-isoxazole (Reiter, L.A, *J. Org. Chem.* **1987**, *52,* 2714-2726) (2.5 g, 25.48 mmol) and cyclohexanone (2.74 g, 28 mmol), the title compound was obtained (4.35 g, 77 %) as a solid.

MS (ESI) *m/z* 223 (M+1).

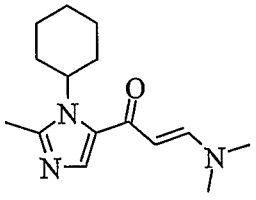
Example 17(b) *5-Acetyl-1-cyclohexyl-2-methyl-1H-imidazole*



The title compound was prepared in accordance with the general method of Example 7(b), with the exception that the product was purified by flash chromatography (CH_2Cl_2/MeOH, 20:1). Using 4-(*N*-acetyl-*N*-cyclohexyl)amino-5-methylisoxazole (4.35 g, 19.6 mmol, obtained from Example 17(a)) the title compound was obtained (1.2 g, 30%) as a yellow oil.

MS (ESI) *m/z* 207 (M+1).

Example 17(c) (2E)-3-Dimethylamino-1-(1-cyclohexyl-2-methyl-1H-imidazol-5-yl)prop-2-en-1-one

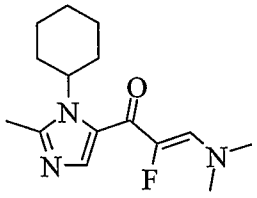


The title compound was prepared in accordance with the general method of Example 7 (c), with the exception that the product was purified by flash chromatography (CH_2Cl_2/MeOH,

25:1). Using 5-acetyl-1-cyclohexyl-2-methyl-1*H*-imidazole (1.2 g, 5.80 mmol, obtained from 17(b)) the title compound was obtained (1.4 g, 93%) as an oil that solidified upon standing.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, J = 12.6 Hz, 1 H), 7.43 (s, 1 H), 5.50 (d, J = 12.6 Hz, 1 H), 5.04–4.90 (m, 1 H), 2.97 (br. s, 6 H), 2.50 (s, 3 H), 2.17-2.02 (m, 2 H), 1.89-1.81 (m, 4 H), 1.72-1.64 (m, 1 H), 1.48-1.19 (m, 3 H); MS (ESI) *m/z* 262 (M+1).

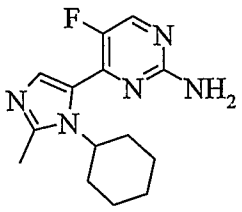
Example 17(d) (2Z)-3-Dimethylamino-2-fluoro-1-(1-cyclohexyl-2-methyl-1H-imidazol-5-yl)prop-2-en-1-one



The title compound was prepared according to the general method of Example 7 (d) with the following modification. The reaction was repeated two times (first with 1.5 equiv. of Selectfluor and then with 0.7 equiv.) in order to get full conversion of the starting material. The product was purified by flash chromatography (CH_2Cl_2/MeOH, 30:1 then 20:1) after every treatment with Selectfluor. Starting from (2*E*)-3-dimethylamino-1-(1-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (1.39 g, 5.32 mmol, obtained from Example 17(c)) the title compound was obtained (0.42 g, 28%).

MS (ESI) *m/z* 280 (M+1).

Example 17(e) 4-(1-Cyclohexyl-2-methyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine

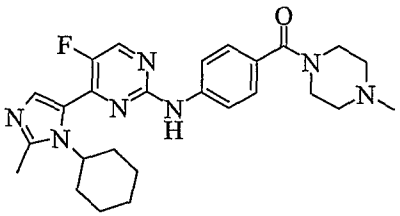


The title compound was prepared in accordance with the general method B with the exception that guanidine carbonate was used. Using (2*Z*)-3-dimethylamino-2-fluoro-1-(1-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)rop-2-en-one (0.42 g, 1.50 mmol, obtained from

Example 17(d)) and guanidine carbonate (0.68 g, 3.76 mmol) the title compound (0.35 g, 85%) was obtained as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, J = 3.3 Hz, 1 H), 7.53 (d, J = 3.9 Hz, 1 H), 4.97-4.81 (m, 3 H), 2.60 (s, 3 H), 2.10-1.91 (m, 6 H), 1.79-1.71 (m, 1 H), 1.43-1.19 (m, 3 H); MS (ESI) *m/z* 276 (M+1).

Example 17(f) 4-(1-Cyclohexyl-2-methyl-1H-imidazol-5-yl)-5-fluoro-N-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride

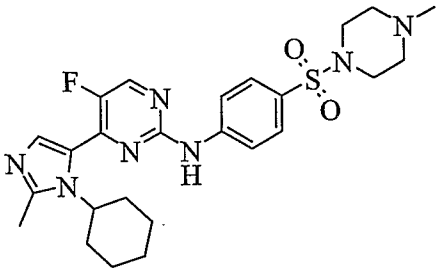


The title compound was prepared in accordance with the general method D, with the exception that the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH gradient; 20:1 to 10:1) before purification by preparative HPLC. Using 4-(1-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (0.075 g, 0.270 mmol, obtained from Example 17(e)), 1-(4-bromobenzoyl)-4-methylpiperazine (0.115 g, 0.405 mmol), sodium tert-butoxide (0.036 g, 0.38 mmol), $Pd(OAc)_2$ (0.012 g, 0.054 mmol) and $Pd(t\text{-}Bu_3P)_2$ (0.14 g, 0.027 mmol), the base of the title compound (0.040 g, 31%) was obtained. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.34 (br s, 1 H), 10.18 (s, 1 H), 8.85 (s, 1 H), 8.11 (s, 1 H), 7.73 (d, J = 8.4 Hz, 2 H), 7.41 (d, J = 8.4 Hz, 2 H), 4.68–4.58 (m, 1 H), 4.20–3.90 (m, 4 H), 3.13–2.97 (m, 2 H), 2.83 (s, 3 H), 2.76 (s, 3 H), 2.00-1.90 (m, 4 H), 1.69-1.57 (m, 2 H), 1.55-1.45 (m, 1 H), 1.20-1.00 (m, 3 H); MS (ESI) *m/z* 478 (M+1).

Example 18

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine hydrochloride



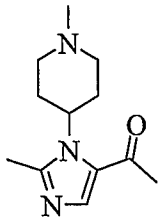
The title compound was prepared in accordance with the general method D, with the exception that the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH/NH_3 aq. 200:10:1) before purification by preparative HPLC. Using 4-(1-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (obtained from Example 17(e)) (0.075 g, 0.270 mmol), 1-(4-bromo-benzenesulfonyl)-4-methylpiperazine (described in WO 2003004472) (0.105 g, 0.320 mmol), sodium tert-butoxide (0.036 g, 0.38 mmol), $Pd(OAc)_2$ (0.012 g, 0.054 mmol) and $Pd(t\text{-}Bu_3P)_2$ (0.14 g, 0.027 mmol), the base of the title compound (0.018 g, 14%) was obtained. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.88 (br s, 1 H), 10.48 (s, 1 H), 8.90 (s, 1 H), 8.10 (s, 1 H), 7.96 (d, J = 8.1 Hz, 2 H), 7.68 (d, J = 8.1 Hz, 2 H), 4.69–4.59 (m, 1 H), 3.76–3.66 (m, 2 H), 3.19–3.05 (m, 2 H), 2.82 (s, 3 H), 2.73 (s, 3 H), 2.02-1.85 (m, 4 H), 1.70-1.60 (m, 2 H), 1.55-1.48 (m, 1 H), 1.25-1.02 (m, 3 H); MS (ESI) *m/z* 514 (M+1).

Example 19

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride

Example 19(a) *5-Acetyl-2-methyl-1-(1-methylpiperidin-4-yl)-1H-imidazole*

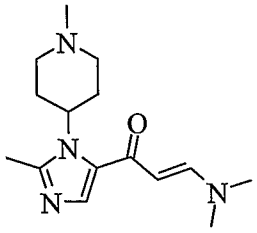


The intermediate acetamide (*N*-(1-aminopiperidin-4-yl)-*N*-isoxazol-4-ylacetamide) was prepared in accordance with the general method of Example 7(a) starting from 5-methyl-4-amino-isoxazole (Reiter, L.A, *J. Org. Chem.*, **1987**, *52,* 2714-2726) (0.61 g, 10.2 mmol),

N-methylpiperidine-4-one (0.63 g, 5.6 mmol) and sodium cyanoborohydride (0.32 g, 5.1 mmol + 0.1 g, 1.6 mmol). The title compound was prepared in accordance with the general method of Example 7(b) using the crude intermediate acetamide (*N*-(1-aminopiperidin-4-yl)-*N*-isoxazol-4-ylacetamide) to give the title compound (0.40 g, 45%) after purification by flash chromatography (CH_2Cl_2/MeOH/NH_3 aq. 150:10:1).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (s, 1 H), 5.28–5.16 (m, 1 H), 3.02–2.92 (m, 2 H), 2.56 (s, 3 H), 2.43 (s, 3 H), 2.40-2.24 (m, 5 H), 2.19-2.06 (m, 2 H), 1.86-1.76 (m, 2 H);
MS (ESI) *m/z* 222 (M+1).

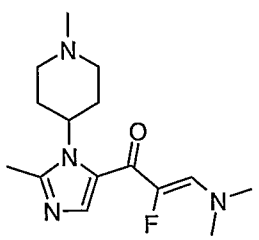
Example 19(b) (2E)-3-Dimethylamino-1-[2-methyl-1-(1-methylpiperidin-4-yl)-1H-imidazol-5-yl]prop-2-en-1-one



The title compound was prepared in accordance with the general method of Example 7(c), using 5-acetyl-2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazole (2.1 g, 9.50 mmol, obtained from Example 19(a)). After purification by flash chromatography (CH_2Cl_2/MeOH/NH_3 aq. gradient; 200:10:1 to 200:15:1.5) the title compound was obtained (1.92 g, 73%) as a yellow oil that solidified upon standing.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (d, J = 12.3 Hz, 1 H), 7.43 (s, 1 H), 5.48 (d, J = 12.3 Hz, 1 H), 5.30–5.18 (m, 1 H), 3.12-2.85 (m, 8 H), 2.54 (s, 3 H), 2.40-2.30 (m, 2 H), 2.29 (s, 3 H), 2.17-2.07 (m, 2 H), 1.88-1.80 (m, 2 H); MS (ESI) *m/z* 277 (M+1).

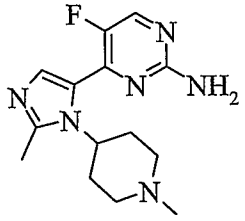
Example 19(c) (2Z)-3-Dimethylamino-2-fluoro-1-[2-methyl-1-(1-methylpiperidin-4-yl)-1H-imidazol-5-yl]prop-2-en-1-one



Selectfluor (2.50 g, 6.95 mmol) was added in portions over 5 minutes to a stirred solution of (2*E*)-3-dimethylamino-1-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one (1.92 g, 6.95 mmol) in MeOH (30 mL) at 0 °C. After stirring for 90 minutes at r.t. more Selectfluor (1.25 g, 3.5 mmol) was added and the mixture was stirred for 2 h. When the reaction was complete it was concentrated *in vacuo*, diluted with NH_3 (3%, aq., 50 mL) and extracted with $CHCl_3$ (3×50mL, contained 5% MeOH). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH/NH_3 aq. 200:10:1), to give the title compound (0.68 g, 33%) as an oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 1 H), 6.85 (d, J = 27.3Hz, 1 H), 4.82–4.70 (m, 1 H), 3.09 (s, 6 H), 3.02-2.92 (m, 2 H), 2.55 (s, 3 H), 2.40-2.25 (m, 5 H), 2.16-2.05 (m, 2 H), 1.91-1.83 (m, 2 H); MS (ESI) *m/z* 295 (M+1).

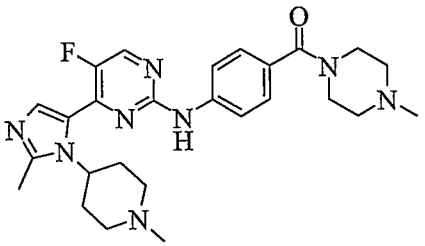
Example 19(d) 5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine



The title compound was prepared in accordance with the general method B with the exception that guanidine carbonate was used. Using (2*Z*)-3-dimethylamino-2-fluoro-1-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one (0.68 g, 2.31 mmol, obtained from Example 19(c)) and guanidine carbonate (1.05 g, 5.78 mmol) the title compound was obtained (0.372 g, 55 %) as a white solid after purification by flash chromatography (CH_2Cl_2/MeOH/NH_3 aq. gradient; 200:10:1 to 100:10:1).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, J = 3 Hz, 1 H), 7.56 (d, J = 3.6 Hz, 1 H), 5.03-2.90 (m, 3 H), 3.05-2.95 (m, 2 H), 2.62 (s, 3 H), 2.52-2.35 (m, 2 H), 2.32 (s, 3 H), 2.12-2.00 (m, 2 H), 1.99-1.90 (m, 2 H); MS (ESI) *m/z* 291 (M+1).

Example 19(e) 5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1H-imidazol-5-yl]-N-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride

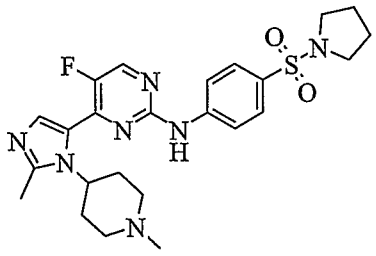


The title compound was prepared in accordance with the general method D, with the exception that the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH/NH_3 aq., 500:30:3) before purification by preparative HPLC. Using 5-fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (0.075 g, 0.256 mmol, obtained from Example 19(d)), 1-(4-bromobenzoyl)-4-methylpiperazine (0.087 g, 0.307 mmol), sodium tert-butoxide (0.036 g, 0.38 mmol), $Pd(OAc)_2$ (0.012 g, 0.054 mmol) and $Pd(t\text{-}Bu_3P)_2$ (0.14 g, 0.027 mmol), the base of the title compound was obtained (0.027 g, 21%). The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.31 (br s, 1 H), 10.22 (s, 1 H), 8.85 (s, 1 H), 8.16 (s, 1 H), 7.81 (d, J = 8.1 Hz, 2 H), 7.43 (d, J = 8.1 Hz, 2 H), 5.14-5.02 (m, 1 H), 3.50–3.35 (m, 4 H), 3.11–2.97 (m, 2 H), 2.91 (s, 3 H), 2.77 (s, 3 H), 2.68 (s, 3 H), 2.35-2.20 (m, 4 H); MS (ESI) *m/z* 493 (M+1).

Example 20

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride



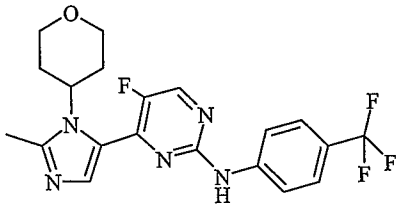
The title compound was prepared in accordance with the general method E, with the exception that the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH/NH_3 aq. 200:10:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 19(d)) (40 mg, 0.136 mmol), 1-(4-bromo-benzenesulfonyl)-pyrrolidine (43 mg, 0.149 mmol), Cs_2CO_3 (50 mg,

0.15 mmol), $Pd_2(dba)_3$ (7 mg, 0.008 mmol) and X-Phos (7 mg, 0.015 mmol), the base of the title compound (58 mg, 85%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.32 (br s, 1 H), 10.48 (s, 1 H), 8.89 (s, 1 H), 8.16 (s, 1 H), 8.00 (d, J = 8.1 Hz, 2 H), 7.73 (d, J = 8.1 Hz, 2 H), 5.16–5.03 (m, 1 H), 3.45–3.35 (m, 2 H), 3.18–3.03 (m, 5 H), 2.91 (s, 3 H), 2.75-2.64 (m, 4 H), 2.35-2.22 (m, 2 H), 2.64 (s, 4 H). MS (ESI) *m/z* 500 (M+1).

Example 21

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(trifluoromethyl)phenyl]pyrimidin-2-amine hydrochloride

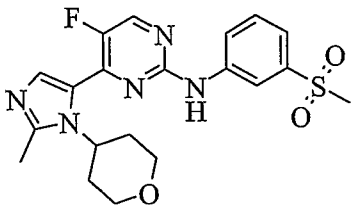


The title compound was prepared in accordance with the general method E, with the exception that the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH 40:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (35 mg, 0.126 mmol), 1-bromo-4-(trifluoromethyl)benzene (0.031 g, 0.139 mmol), Cs_2CO_3 (92 mg, 0.28 mmol), $Pd_2(dba)_3$ (7 mg, 0.008 mmol) and X-Phos (7 mg, 0.014 mmol), the base of the title compound (50 mg, 92%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.28 (s, 1 H), 8.87 (s, 1 H), 8.10 (s, 1 H), 7.84 (d, J = 8.1 Hz, 2 H), 7.64 (d, J = 8.1 Hz, 2 H), 5.05–4.93 (m, 1 H), 3.84–3.77 (m, 2 H), 3.20–3.10 (m, 2 H), 2.83 (s, 3 H), 2.20-2.11 (m, 2 H), 1.98-1.90 (m, 2 H); MS (ESI) *m/z* 422 (M+1).

Example 22

5-Fluoro-*N*-[3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride

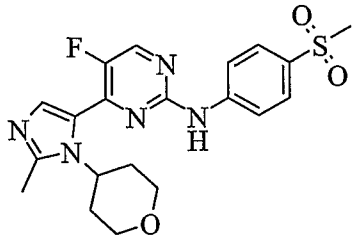


The title compound was prepared in accordance with the general method E, with the exception that the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH 25:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example7 (e)) (35 mg, 0.126 mmol), 1-bromo-3-(methylsulfonyl)benzene (0.030 g, 0.126 mmol), Cs_2CO_3 (92 mg, 0.28 mmol), $Pd_2(dba)_3$ (7 mg, 0.008 mmol) and X-Phos (7 mg, 0.014 mmol), the base of the title compound (44 mg, 81%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.19 (s, 1 H), 8.86 (s, 1 H), 8.17 (s, 1 H), 8.09 (s, 1 H), 8.01 (d, J = 6.8 Hz, 1 H), 7.62–7.52 (m, 2 H), 5.03–4.91 (m, 1 H), 3.87–3.79 (m, 2 H), 3.24-3.10 (m, 5 H), 2.82 (s, 3 H), 2.20-2.10 (m, 2 H), 1.97-1.90 (m, 2 H). MS (ESI) *m/z* 432 (M+1).

Example 23

5-Fluoro-*N*-[4-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride



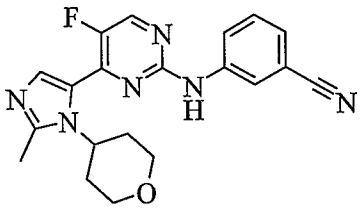
The title compound was prepared in accordance with the general method E, with the exception that the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH 20:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (35 mg, 0.126 mmol), 1-chloro-4-(methylsulfonyl)benzene (0.0215 g, 0.113 mmol), Cs_2CO_3 (92 mg, 0.28 mmol), $Pd_2(dba)_3$ (7 mg, 0.008 mmol) and X-Phos (7 mg, 0.014 mmol), the base of the title

compound (45 mg, 94%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.39 (s, 1 H), 8.89 (s, 1 H), 8.10 (s, 1 H), 7.88 (d, J = 8.6 Hz, 2 H), 7.81 (d, J = 8.6 Hz, 2 H), 5.03–4.92 (m, 1 H), 3.87–3.79 (m, 2 H), 3.25-3.10 (m, 5 H), 2.83 (s, 3 H), 2.21-2.10 (m, 2 H), 1.98-1.91 (m, 2 H). MS (ESI) *m/z* 432 (M+1).

Example 24

3-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzonitrile hydrochloride



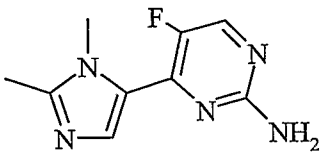
The title compound was prepared in accordance with the general method E, with the exception that the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH 40:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (35 mg, 0.126 mmol), 3-bromobenzonitrile (0.023 g, 0.126 mmol), Cs_2CO_3 (92 mg, 0.28 mmol), $Pd_2(dba)_3$ (7 mg, 0.008 mmol) and X-Phos (7 mg, 0.014 mmol), the base of the title compound (44 mg, 92%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.22 (s, 1 H), 8.87 (s, 1 H), 8.18-8.05 (m, 2 H), 7.90 (s, 1 H), 7.55-7.25 (m, 2 H), 5.03–4.91 (m, 1 H), 3.85–3.77 (m, 2 H), 3.22–3.10 (m, 2 H), 2.83 (s, 3 H), 2.21-2.11 (m, 2 H), 1.97-1.90 (m, 2 H). MS (ESI) *m/z* 379 (M+1).

Example 25

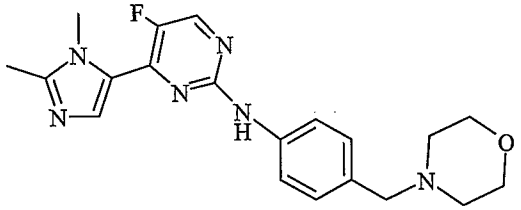
4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride

Example 25(a) *4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine*



2-Chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (0.295 g, 1.30 mmol) (obtained from Example 1(b)) was dissolved in 1-propanol (3.0 mL) in a microwave vial. Ammonium hydroxide (28%, 1.0 mL) was added, the vial was sealed and the mixture heated in a microwave oven (+140 °C, 4h). The reaction mixture was cooled to r.t. and the solvent was evaporated. The residue was partitioned between CH_2Cl_2 and 1M aqueous HCl. The aqueous phase, containing the product, was neutralized with saturated aqueous $NaHCO_3$ and the product extracted with CH_2Cl_2. The organic phase was co-evaporated with ethanol and the residue was purified by flash chromatography using (CH_2Cl_2/MeOH gradient; 100:1 to 94:6) to give the title compound (0.210 g, 78%) as a solid.
^{1}H NMR ($CDCl_3$) δ ppm 8.15 (d, *J*=3.5 Hz, 1 H), 7.71 (d, *J*=4.3 Hz, 1 H), 4.87 (br s, 2 H), 3.97 (s, 3 H), 2.49 (s, 3 H); MS (ESI) *m/z* 208 (M+1).

Example 25(b) 4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoro-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride

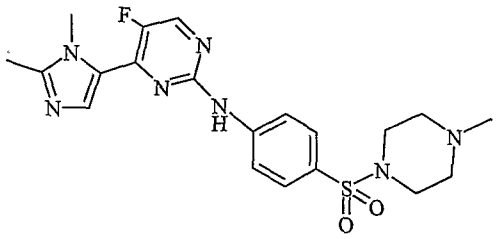


The title compound was prepared in accordance with the general method E. Using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (21 mg, 0.10 mmol, obtained from Example 25(a)), 4-(4-bromobenzyl)morpholine (28 mg, 0.11 mmol), Cs_2CO_3 (58 mg, 0.18 mmol), $Pd_2(dba)_3$ (7 mg, 0.007 mmol) and X-Phos (8 mg, 0.017 mmol), the base of the title compound was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D, with the exceptions that dilute ammonium hydroxide was used instead of dilute $NaHCO_3$ in the washing of the organic phase. The organic phase was co-evaporated with absolute ethanol instead of drying with Na_2SO_4 before evaporation, and the precipitated salt was collected by filtration and re-dissolved in water before freeze drying, giving the title compound (28 mg, 61%) as a yellow solid.

^{1}H NMR (DMSO-d_6) δ ppm 10.84 (br s, 1 H), 10.02 (s, 1 H), 8.75 (d, *J*=2.5 Hz, 1 H), 8.15 (d, *J*=2.5 Hz, 1 H), 7.75 (d, *J*=8.5 Hz, 2 H), 7.51 (d, *J*=8.5 Hz, 2 H), 4.26 (s, 2 H), 4.01 (s, 3 H), 3.99-3.86 (m, 2 H), 3.76 (t, *J*=11.8 Hz, 2 H), 3.25-3.14 (m, 2 H), 3.13-2.96 (m, 2 H), 2.66 (s, 3 H); MS (ESI) *m/z* 381 (M+1).

Example 26

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine

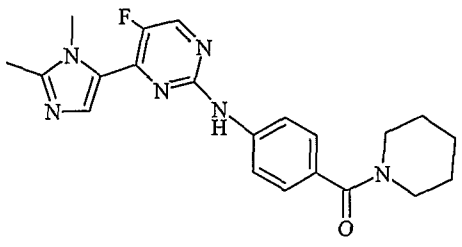


The title compound was prepared in accordance with the general method E. Using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (obtained from Example 25(a)) (23 mg, 0.11 mmol), 1-[(4-bromophenyl)sulfonyl]-4-methylpiperazine (37 mg, 0.11 mmol), Cs_2CO_3 (59 mg, 0.18 mmol), $Pd_2(dba)_3$ (6 mg, 0.006 mmol) and X-Phos (6 mg, 0.013 mmol), the base of the title compound was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the procedure described in Example 25 (b), giving the title compound (33 mg, 57%) as a yellow solid.

^{1}H NMR (DMSO-d_6) δ ppm 10.44 (br s, 1 H), 10.42 (s, 1 H), 8.82 (d, *J*=2.5 Hz, 1 H), 8.13 (br s, 1 H), 7.99 (d, *J*=8.8 Hz, 2 H), 7.73 (d, *J*=8.8 Hz, 2 H), 4.03 (s, 3 H), 3.83-3.63 (m, 2 H), 3.23-3.02 (m, 4 H), 2.74 (s, 3 H), 2.65 (s, 3 H), 2.70-2.56 (m, 2 H); MS (ESI) *m/z* 446 (M+1).

Example 27

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-2-amine hydrochloride

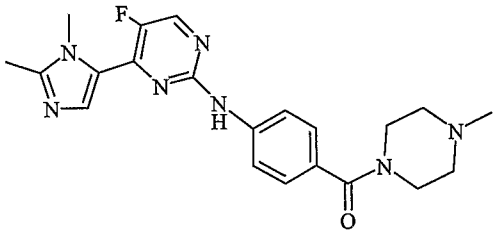


The title compound was prepared in accordance with the general method E. Using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (obtained from Example25 (a)) (25 mg, 0.12 mmol), 1-(4-bromobenzoyl)piperidine (33 mg, 0.12 mmol), Cs_2CO_3 (66 mg, 0.20 mmol), $Pd_2(dba)_3$ (6 mg, 0.007 mmol) and X-Phos (6 mg, 0.013 mmol), the base of the title compound was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the procedure described in Example 25(b), giving the title compound (35 mg, 61%) as a white solid.

^{1}H NMR (DMSO-d_6) δ ppm 10.04 (s, 1 H), 8.77 (d, *J*=2.8 Hz, 1 H), 8.17 (d, *J*=2.8 Hz, 1 H), 7.73 (d, *J*=8.5 Hz, 2 H), 7.35 (d, *J*=8.8 Hz, 2 H), 4.02 (s, 3 H), 3.50-3.41 (m, 4 H), 2.66 (s, 3 H), 1.67-1.57 (m, 2 H), 1.57-1.42 (m, 4 H); MS (ESI) *m/z* 395 (M+1).

Example 28

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride

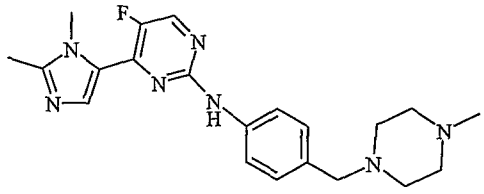


The title compound was prepared in accordance with the general method E. Using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (obtained from Example 25(a)) (18 mg, 0.089 mmol), 1-(4-bromobenzoyl)-4-methylpiperazine (25 mg, 0.089 mmol), Cs_2CO_3 (42 mg, 0.13 mmol), $Pd_2(dba)_3$ (4 mg, 0.004 mmol) and X-Phos (4 mg, 0.009 mmol), the base of the title compound was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the procedure described in Example 25 (b), giving the title compound (28 mg, 64%) as a yellow solid.

^{1}H NMR (DMSO-d_6) δ ppm 10.71 (br s, 1 H), 10.13 (s, 1 H), 8.78 (d, *J*=2.8 Hz, 1 H), 8.18 (d, *J*=2.5 Hz, 1 H), 7.78 (d, *J*=8.5 Hz, 2 H), 7.45 (d, *J*=8.5 Hz, 2 H), 4.20 (br s, 2 H), 4.03 (s, 3 H), 3.07 (br s, 2 H), 2.79 (s, 3 H), 2.67 (s, 3 H); MS (ESI) *m/z* 410 (M+1).

Example 29

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}pyrimidin-2-amine hydrochloride

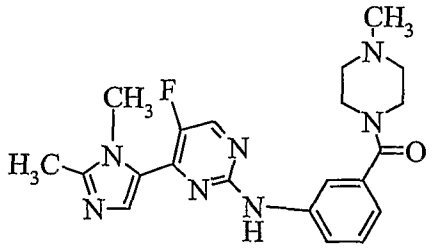


The title compound was prepared in accordance with the general method E. Using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (obtained from Example25 (a)) (19 mg, 0.091 mmol), 1-(4-bromobenzyl)-4-methylpiperazine (Organ, M.G. et al, *J. Comb. Chem.* **2001**, *3*, 473-476) (28 mg, 0.10 mmol), Cs_2CO_3 (42 mg, 0.13 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol) and X-Phos (4 mg, 0.009 mmol), the base of the title compound was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the procedure described in Example 25 (b), giving the title compound (28 mg, 61%) as a yellow solid.

^{1}H NMR (DMSO-d_6) δ ppm 10.00 (br s, 1 H), 8.76 (d, *J*=2.5 Hz, 1 H), 8.20 (d, *J*=2.8 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 2 H), 7.55 - 7.38 (m, 2 H), 4.02 (s, 3 H), 4.02 (br s, 1 H), 2.79 (s, 3 H), 2.68 (s, 3 H); MS (ESI) *m/z* 396 (M+1).

Example 30

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride



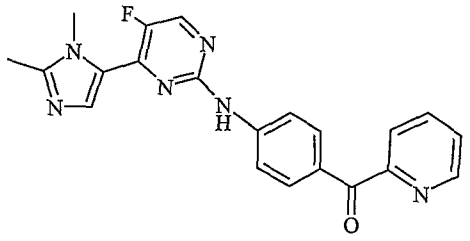
The title compound was prepared in accordance with the general method E. Using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (obtained from Example 25 (a)) (18 mg, 0.084 mmol), 1-(3-chlorobenzoyl)-4-methylpiperazine (21 mg, 0.87 mmol), Cs_2CO_3 (43 mg, 0.13 mmol), $Pd_2(dba)_3$ (4 mg, 0.004 mmol) and X-Phos (4 mg, 0.009

mmol), the base of the title compound was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the procedure described in Example 25 (b), giving the title compound (13 mg, 32%) as a yellow solid.

^{1}H NMR (DMSO-d_6) δ ppm 10.69 (br s, 1 H), 10.00 (s, 1 H), 8.74 (d, J=2.5 Hz, 1 H), 8.12 (br s, 1 H), 7.83-7.72 (m, 2 H), 7.42 (t, J=7.9 Hz, 1 H), 7.09 (d, J=7.5 Hz, 1 H), 4.50 (br s, 1 H), 4.01 (s, 3 H), 2.80 (s, 3 H), 2.65 (s, 3 H); MS (ESI) m/z 410 (M+1).

Example 31

(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(pyridin-2-yl)methanone hydrochloride

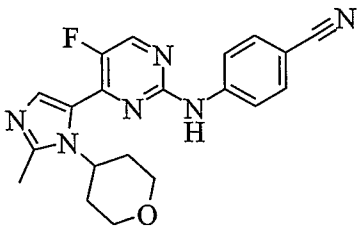


The title compound was prepared in accordance with the general method E. Using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (obtained from Example 25(a)) (23 mg, 0.11 mmol), (4-bromophenyl)(pyridin-2-yl)methanone (29 mg, 0.11 mmol), Cs_2CO_3 (72 mg, 0.22 mmol), $Pd_2(dba)_3$ (6 mg, 0.007 mmol) and X-Phos (7 mg, 0.016 mmol), the base of the title compound was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the procedure described in Example 25(b), giving the title compound (28 mg, this compound appeared to be a non-stoichiometric salt, gives an estimated yield of 55%) as a yellow solid.

^{1}H NMR (DMSO-d_6) δ ppm 10.36 (s, 1 H), 8.84 (d, J=2.5 Hz, 1 H), 8.75-8.69 (m, 1 H), 8.20 (d, J=2.8 Hz, 1 H), 8.09 - 8.00 (m, 3 H), 7.92 (d, J=7.8 Hz, 1 H), 7.87 (d, J=8.8 Hz, 2 H), 7.68-7.62 (m, 1 H), 4.04 (s, 3 H), 2.67 (s, 3 H); MS (ESI) m/z 389 (M+1).

Example 32

4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzonitrile hydrochloride



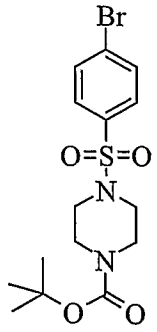
The title compound was prepared in accordance with the general method E, with the exception that the base of the product was purified by flash chromatography (CH_2Cl_2/MeOH 30:1). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (35 mg, 0.126 mmol), 4-chlorobenzonitrile (15.5 g, 0.113 mmol), Cs_2CO_3 (92 mg, 0.28 mmol), $Pd_2(dba)_3$ (7 mg, 0.008 mmol) and X-Phos (7 mg, 0.014 mmol), the base of the title compound (38 mg, 88%) was obtained as a solid. The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.42 (s, 1 H), 8.90 (s, 1 H), 8.09 (s, 1 H), 7.86 (d, J = 8.5 Hz, 2 H), 7.74 (d, J = 8.5 Hz, 2 H), 5.04–4.92 (m, 1 H), 3.89–3.81 (m, 2 H), 3.26–3.16 (m, 2 H), 2.83 (s, 3 H), 2.20-2.12 (m, 2 H), 1.97-1.90 (m, 2 H); MS (ESI) *m/z* 379 (M+1).

Example 33

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(piperazin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride

Example 33(a) 1-(tert-Butoxycarbonyl)-4-(4-bromo-benzenesulfonyl)-piperazine

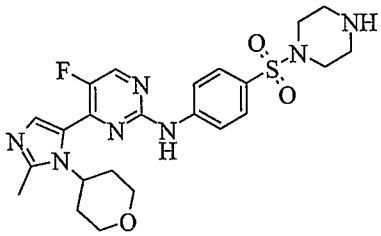


N-boc-Piperazine (0.5 g, 2.68 mmol) and diisopropyethylamine (0.69 g, 5.36 mmol) were dissolved in CH_2Cl_2 (50 mL) and cooled to 0°C. 4-Bromo-phenylsulphonyl chloride (0.68 g, 2.68 mmol) in CH_2Cl_2 (10 mL) was added dropwise under vigorous stirring. After stirring for 15h at r.t. the reaction mixture was washed with saturated aqueous $NaHCO_3$

(2×20 mL), brine, then dried (Na_2SO_4) and concentrated to dryness. The solid residue was recrystallized from heptane/EtOAc mixture (2:1), filtered and washed with cold heptane. The title compound was obtained (0.8 g, 74%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 8.4 Hz, 2 H), 3.54–3.47 (m, 4 H), 3.01–2.94 (m, 4 H), 1.41 (s, 9 H).

Example 33(b) 5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(piperazin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride



5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (45 mg, 0.162 mmol) and 1-(*tert*-butoxycarbonyl)-4-(4-bromo-benzenesulfonyl)-piperazine (62 mg, 0.154 mmol) were dissolved in dioxane (3 mL). Cesium carbonate (105 mg, 0.324 mmol) was added and nitrogen gas was bubbled throw the stirred suspension for 2-3 min followed by the addition of $Pd_2(dba)_3$ (7.5 mg, 0.0081 mmol) and X-Phos (7.7 g, 0.0162 mmol). The vessel was closed and heated to +90 °C and stirred at this temperature for 20 h. The cooled mixture was diluted with chloroform (15 ml) and water (20 mL), the aqueous layer was separated and extracted with chloroform (20mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography using CH_2Cl_2/MeOH (40:1) as eluent. Product-containing fractions were concentrated, dissolved in MeOH (20 mL) and treated with HCl (37% aqueous, 0.5 mL). The mixture was stirred overnight at r.t. and concentrated to dryness. Diluted with chloroform (20 mL) and water (20 mL) and the aqueous layer was separated and extracted with chloroform (3×20mL). The combined organic layers were dried (Na_2SO_4), the solvents were removed *in vacuo* and the residue was purified by flash chromatography using CH_2Cl_2/MeOH/aqueous NH_3 (150:10:1 to 100:10:1) as eluent, obtaining the base (22 mg, 28 %) as an oil. The base of the title compound was dissolved in chloroform/ether (1:1) and treated with 1M HCl in ether. The

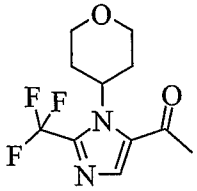
resulting precipitate was collected by filtration and washed with ether to obtain of the title compound (13 mg) as a solid.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.45 (s, 1 H), 9.12 (br s, 1 H), 8.90 (s, 1 H), 8.07 (s, 1 H), 7.96 (d, J = 8.7 Hz, 2 H), 7.70 (d, J = 8.7 Hz, 2 H), 5.03–4.93 (m, 1 H), 3.89–3.81 (m, 2 H), 3.65–3.40 (m, 2 H), 3.28–3.09 (m, 8 H), 2.82 (s, 3 H), 2.22-2.10 (m, 2 H), 2.00-1.92 (m, 2 H); MS (ES) *m/z* 502 (M+1).

Example 34

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride

Example 34(a) 5-Acetyl-1-(tetrahydro-2H-pyran-4-yl)- 2-trifluoromethyl-1H-imidazole

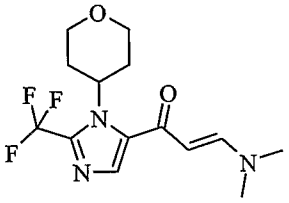


5-Methyl-4-amino-isoxazole (1.7 g, 17.25 mmol) and acetic acid (1.1 g, 19 mmol) were dissolved in methanol (50 mL). Tetrahydro-2*H*-pyran-4-one (1.9 g, 19 mmol) was added and the mixture was cooled to 0 – (-5) °C and stirred for 1 h. Sodium cyanoborohydride (0.812 g, 12.9 mmol) was added in portions to the reaction mixture at –5 °C, causing weak exothermic and gas evolution. The cooling bath was removed and the mixture was stirred at r.t. for 2 h followed by addition of water (20 mL). The methanol was removed from the reaction mixture by vacuum distillation, and the intermediate amine was extracted with ethyl acetate (3×80 mL). The combined organic layers were dried (Na_2SO_4), concentrated to dryness, dissolved in toluene and re-concentrated. The crude intermediate amine, was dissolved in CH_2Cl_2 (20 mL) and pyridine (2 mL, 26 mmol) was added. The mixture was cooled to 0°C and trifluoroacetic anhydride (4.35 g, 20.7 mmol) was added dropwise. The mixture was continued stirring for 2 h at r.t. then washed with water and saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2×30 mL), the organic extracts were dried (Na_2SO_4) and concentrated to dryness to give a second crude intermediate, 4-[*N*-(tetrahydro-2*H*-pyran-4-yl)]-*N*-trifluoroacetyl-amino-5-methylisoxazole. MS (ES) *m/z* 279 (M^++1). The title compound was prepared in accordance with the general method of

Example 7 (b) using the intermediate 4-[*N*-(tetrahydro-2*H*-pyran-4-yl)]-*N*-trifluoroacetyl-amino-5-methylisoxazole (max 17.25 mmol), with the exception that the product was purified by flash chromatography (heptane/EtOAc 3:2), giving the title compound (3.03 g, 67%) as an oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (s, 1 H), 4.89-4.75 (m, 1 H), 4.17–4.07 (m, 2 H), 3.54-3.44 (m, 2 H), 2.75-2.60 (m, 2 H), 2.56 (s, 3 H), 1.72-1.63 (m, 2 H);
MS (ES) *m/z* 263 (M+1).

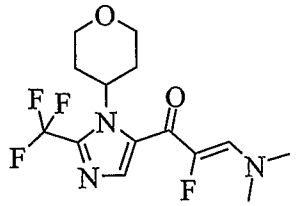
(b) (2E)-3-Dimethylamino-1-[1-(tetrahydro-2H-pyran-4-yl)-2-trifluoromethyl-1H-imidazol-5-yl]prop-2-en-1-one



The title compound was prepared in accordance with the general method of Example 7 (c), with the exception that the product was purified by flash chromatography (EtOAc). Using 5-acetyl-1-(tetrahydro-2*H*-pyran-4-yl)- 2-trifluoromethyl-1*H*-imidazole (3.03 g, 11.55 mmol, obtained from Example 34(a)) the title compound was obtained (3.2 g, 87 %) as an oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, J = 12.3 Hz, 1 H), 7.49 (s, 1 H), 5.50 (d, J = 12.3 Hz, 1 H), 4.89-4.75 (m, 1 H), 4.14–4.05 (m, 2 H), 3.54-3.44 (m, 2 H), 3.16 (br. s, 3 H), 2.93 (br. s, 3 H), 2.86-2.72 (m, 2 H), 1.80-1.72 (m, 2 H); MS (ES) *m/z* 318 (M+1).

Example 34(c) (2Z)-3-Dimethylamino-2-fluoro-1-[1-(tetrahydro-2H-pyran-4-yl)-2-trifluoromethyl-1H-imidazol-5-yl]prop-2-en-1-one



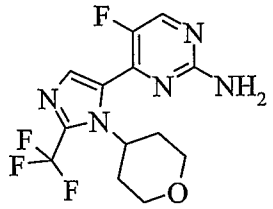
Selectfluor (0.370 g, 1.04 mmol) was added in portions to a stirred solution of (2*E*)-3-dimethylamino-1-[1-(tetrahydro-2*H*-pyran-4-yl)-2-trifluoromethyl-1*H*-imidazol-5-yl]prop-

2-en-1-one (0.300 g, 0.946 mmol, obtained from Example 34(b)) in MeCN (20 mL) at 0 °C. After stirring for 0.5 h at r.t. more Selectfluor (0.050 g, 0.14 mmol) was added, and the mixture was stirred for 0.5 h. The solvent was evaporated *in vacuo*, diluted with 3% aqueous NH_3 (20 mL) and extracted with $CHCl_3$ (3×20mL). The organic extracts were dried (Na_2SO_4), evaporated *in vacuo* and the crude product was purified by flash chromatography (heptane/EtOAc 1:2), followed by neat EtOAc) to obtain the title compound (0.170 g, 53 %) as an oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (s, 1 H), 6.85 (d, J = 26.7 Hz, 1 H), 4.67–4.54 (m, 1 H), 4.11–4.03 (m, 2 H), 3.50-3.38 (m, 2 H), 3.14 (s, 6 H), 2.72-2.56 (m, 2 H), 1.83-1.74 (m, 2 H);

MS (ES) *m/z* 336 (M+1).

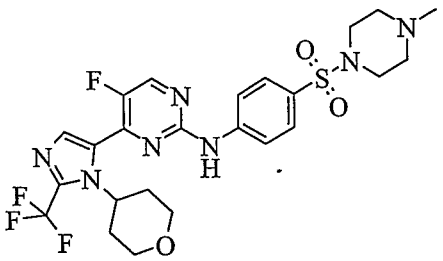
Example 34(d) 5-Fluoro-4-[1-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine



The title compound was prepared in accordance with the general method B with the exception that guanidine carbonate was used. Using (2*Z*)-3-dimethylamino-2-fluoro-1-[1-(tetrahydro-2*H*-pyran-4-yl)-2-trifluoromethyl-1*H*-imidazol-5-yl]prop-2-en-1-one (0.330 g, 1.0 mmol, obtained from Example 34(c)) and guanidine carbonate (0.45 g, 2.50 mmol). After purification by flash chromatography (heptane/EtOAc 1:2), the title compound was obtained (0.170 g, 51 %) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1 H), 7.63 (d, J = 2.7 Hz, 1 H), 5.10 (br.s., 2 H), 4.88–4.76 (m, 1 H), 4.16–4.07 (m, 2 H), 3.53-3.42 (m, 2 H), 2.80-2.65 (m, 2 H), 1.89-1.81 (m, 2 H); MS (ES) *m/z* 332 (M+1).

Example 34(e) 5-Fluoro-N-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[1-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride

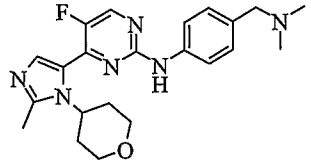


The title compound was prepared in accordance with the general method of Example 33(b). Using 5-fluoro-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (33 mg, 0.100 mmol, obtained from Example 34(d)) and 1-(4-bromo-benzenesulfonyl)-4-methylpiperazine (described in WO 2003004472) (29 mg, 0.090 mmol), the base of the title compound was obtained (48 mg, 94 %) after purification by flash chromatography (CH_2Cl_2/MeOH 30:1 to 15:1). The hydrochloride of the title compound was prepared in accordance with the general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.68 (br s, 1 H), 10.41 (s, 1 H), 8.87 (s, 1 H), 7.97 (d, J = 8.4 Hz, 2 H), 7.71 (d, J = 8.4 Hz, 2 H), 7.57 (s, 1 H), 4.84–4.75 (m, 1 H), 3.89–3.80 (m, 2 H), 3.77–3.68 (m, 2 H), 3.47–3.39 (m, 2 H), 3.33–3.23 (m, 2 H), 3.16–3.08 (m, 2 H), 2.73 (s, 3 H), 2.68–2.59 (m, 2 H), 2.20-2.10 (m, 2 H), 1.97-1.90 (m, 2 H); MS (ES) *m/z* 570 (M+1).

Example 35

N-{4-[(Dimethylamino)methyl]phenyl}-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine



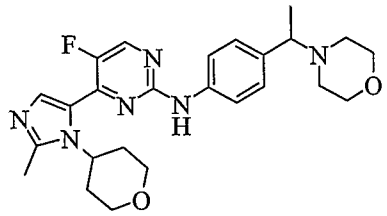
5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine (50 mg, 180 μmol, obtained from 7(e)) and 1-(4-bromophenyl)-N,N-dimethylmethanamine (38.6 mg, 180 μmol) in dry dioxane (2.3 mL) were purged with Ar (gas) for 10 min. $Pd_2(dba)_3$ (8.3 mg, 9 μmol), X-Phos (8.6 mg, 18 μmol) and Cs_2CO_3 (102 mg, 289 μmol) were added and Ar (gas) was bubbled through the mixture for 5 min prior to heating at +90 °C for 47 h. The mixture was allowed to cool, diluted with CH_2Cl_2 and filtered through diatomaceous earth. The organics were washed with water, dried (Na_2SO_4), filtered and

concentrated. The crude was purified by flash silica gel chromatography $CHCl_3$/MeOH 9:1 - 4:1 to give 50 mg (68%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1 H), 8.56 (d, 1 H), 7.53 (d, 2 H), 7.34 (d, 1 H), 7.18 (d, 2 H), 5.04 (m, 1 H), 3.79 (m, 2 H), 3.35 (s, 2 H), 3.06 (t, 2 H), 2.53 (s, 3 H), 2.21-2.11 (m, 8 H), 1.78 (m, 2 H); MS (ES) m/z 409 (M-1).

Example 36

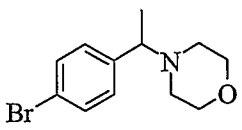
5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(1-morpholin-4-ylethyl)phenyl]pyrimidin-2-amine



5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine (50 mg, 180 µmol, obtained from Example 7(e)) and 4-[1-(4-bromophenyl)ethyl]morpholine (obtained from Example 36(a)) (48.7 mg, 180 µmol) in dry dioxane (2.3 mL) were purged with Ar (gas) for 10 min. $Pd_2(dba)_3$ (8.3 mg, 9 µmol), X-Phos (8.6 mg, 18 µmol) and Cs_2CO_3 (102 mg, 289 µmol) were added and Ar (g) was bubbled through the mixture for 5 min prior to heating at +90 °C for 45 h. The mixture was allowed to cool, diluted with CH_2Cl_2 and filtered through diatomaceous earth. The organics were washed with water, dried (Na_2SO_4), filtered and concentrated. The crude was purified twice by flash silica gel chromatography $CHCl_3$/MeOH 20:1 and EtOAc/MeOH 40:1 - 20:1 to give 53 mg of the title compound (63%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1 H), 8.55 (d, 1 H), 7.52 (d, 2 H), 7.33 (d, 1 H), 7.18 (d, 2 H), 5.05 (m, 1 H), 3.80 (m, 2 H), 3.54 (t, 4 H), 3.28 (q, 1 H), 3.08 (t, 2 H), 2.53 (s, 3 H), 2.37 (m, 2 H), 2.28-2.11 (m, 4 H), 1.78 (m, 2 H), 1.26 (d, 3 H); MS (ES) m/z 465 (M-1).

Example 36(a) *4-[1-(4-Bromophenyl)ethyl]morpholine*

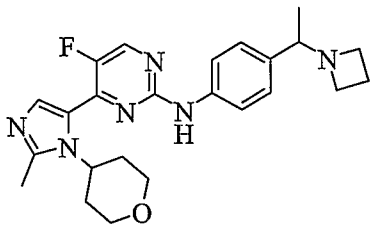


DIPEA (1.98 mL, 11.4 mmol) and morpholine (398 µL, 4.56 mmol) were added to 1-bromo-4-(1-chloroethyl)benzene (Woolman et al. *J. Chem. Soc.* **1943**, 99-101) (500 mg, 2.28 mmol) in dry MeCN (2.5 mL) and the solution was heated at +60 °C for 72 h. The mixture was allowed to cool, concentrated and diluted in CH_2Cl_2. The organics were washed by water, brine and water, dried (Na_2SO_4), filtered and concentrated to give 616 mg (100%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (m, 2 H), 7.26 (m, 2 H), 3.54 (m, 4 H), 3.33 (q, 1 H), 2.38 (m, 2 H), 2.24 (m, 2 H), 1.24 (d, 3 H); MS (ES) m/z 270/272 (M/M+2).

Example 37

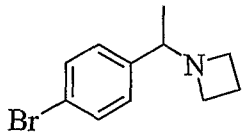
N-[4-(1-Azetidin-1-ylethyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine



5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine (50 mg, 180 µmol, obtained from Example 7(e)) and 1-[1-(4-bromophenyl)ethyl]azetidine (obtained from Example 37(a)) (43.3 mg, 180 µmol) in dry dioxane (2.3 mL) were purged with Ar (gas) for 10 min. $Pd_2(dba)_3$ (8.3 mg, 9 µmol), X-Phos (8.6 mg, 18 µmol) and Cs_2CO_3 (102 mg, 289 µmol) were added and Ar (g) was bubbled through the mixture for 5 min prior to heating at +90 °C for 51 h. The mixture was allowed to cool, diluted with CH_2Cl_2 and filtered through diatomaceous earth. The organics were washed with water, dried (Na_2SO_4), filtered and concentrated. The crude was purified by flash silica gel chromatography $CHCl_3$/MeOH 9:1- 3:1 to give 40 mg (51%).

^{1}H NMR (600 MHz, CD_3OD) δ 8.39 (d, 1 H), 7.55 (d, 2 H), 7.42 (d, 1 H), 7.26 (d, 2 H), 5.21 (m, 1 H), 3.91 (m 2 H), 3.52 (m, 1 H), 3.41 (m, 2 H), 3.25 (m, 2 H), 3.19 (t, 2 H), 2.61 (s, 3 H), 2.34 (m, 2 H), 2.11 (quintet, 2 H), 1.86 (m, 2 H), 1.27 (d, 3 H); MS (ES) m/z 435 (M-1).

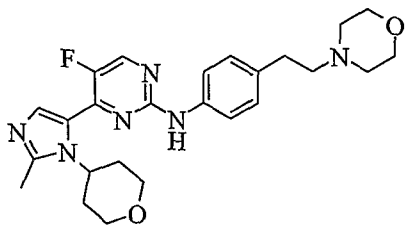
Example 37(a) *1-[1-(4-Bromophenyl)ethyl]azetidine*



DIPEA (1.98 mL, 11.4 mmol) and azetidine (307 µL, 4.56 mmol) were added to 1-bromo-4-(1-chloroethyl)benzene (Woolman et al. *J. Chem. Soc.* **1943**, 99-101) (500 mg, 2.28 mmol) in dry MeCN (2.5 mL) and the solution was heated at +60 °C for 74 h. More azetidine (100 µL, 1.48 mmol) was added, and after heating for 23 more hours. even more azetidine (100 µL, 1.48 mmol) and DIPEA (500 µL, 2.87 mmol) were added and the mixture was heated for a further 27 h. After cooling and concentration the crude was diluted with CH_2Cl_2. The organics were washed with water, brine and water, dried (Na_2SO_4), filtered and concentrated to give 481 mg (87%) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (m, 2 H), 7.24 (m, 2 H), 3.22 (q, 1 H), 3.04 (m, 2 H), 2.96 (m, 2 H), 1.88 (quintet, 2 H), 1.05 (d, 3 H); MS (ES) m/z 240/242 (M/M+2).

Example 38

5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(2-morpholin-4-ylethyl)phenyl]pyrimidin-2-amine



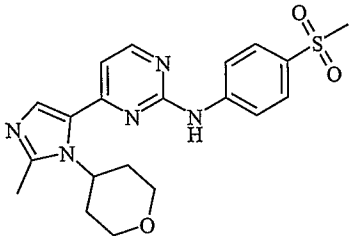
5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine (50 mg, 180 µmol, obtained from Example 7(e)) and 4-[2-(4-bromophenyl)ethyl]morpholine (King et al. *Tet. Lett.* **2005**, 46, 1471-1474) (48.7 mg, 180 µmol) in dry dioxane (2.3 mL) were purged with Ar (gas) for 10 min. $Pd_2(dba)_3$ (8.3 mg, 9 µmol), X-Phos (8.6 mg, 18 µmol) and Cs_2CO_3 (102 mg, 289 µmol) were added and Ar (g) was bubbled through the mixture for 5 min prior to heating at +90 °C for 72 h. The mixture was allowed to cool, diluted with CH_2Cl_2 and filtered through diatomaceous earth. The organics were washed with water, dried (Na_2SO_4), filtered and concentrated. The crude was purified by flash silica gel chromatography EtOAc/MeOH 20:1- 5:1, the residue was

dissolved in $CHCl_3$ and filtered through tightly packed glass wool and concentrated to give 41 mg of the title compound (49%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1 H), 8.53 (d, 1 H), 7.46 (d, 2 H), 7.33 (d, 1 H), 7.12 (d, 2 H), 5.03 (m, 1 H), 3.80 (m, 2 H), 3.57 (t, 4 H), 3.03 (t, 2 H), 2.68 (t, 2 H), 2.53 (s, 3 H), 2.47 (m, 2 H), 2.41 (m, 4 H), 2.15 (m, 2 H), 1.76 (m, 2 H); MS (ES) m/z 467 (M+1).

Example 39

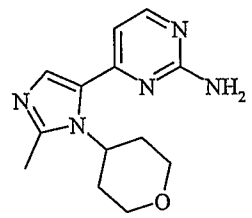
***N*-[4-(Methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**



The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 39(a)) (60.4 mg, 0.233 mmol), 1-bromo-4-(methylsulfonyl)benzene (54.8 mg, 0.233 mmol), Cs_2CO_3 (152 mg, 0.466 mmol), $Pd_2(dba)_3$ (5 mg, 0.006 mmol) and X-Phos (7 mg, 0.012 mmol) to give the title compound (48 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.43 (d, *J*=5.3 Hz, 1 H) 7.96 (s, 1 H) 7.78 - 7.88 (m, 4 H) 7.43 (s, 1 H) 7.02 (d, *J*=5.3 Hz, 1 H) 5.12 - 5.24 (m, 1 H) 4.04 (dd, *J*=11.5, 4.4 Hz, 2 H) 3.24 - 3.34 (m, 2 H) 3.04 (s, 3 H) 2.61 (s, 3 H) 2.39 - 2.53 (m, 2 H) 1.85 (dd, *J*=12.4, 2.8 Hz, 2 H); MS (ESI) *m/z* 414 (M + 1).

Example 39(a) 4-[2-Methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine

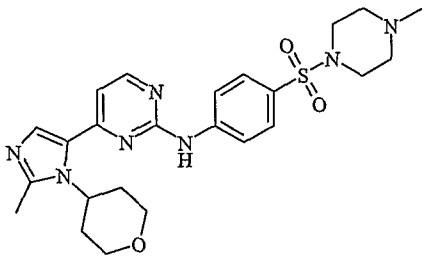


(2*E*)-3-Dimethylamino-1-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one (described within WO 2005101997) (1.824 g, 6.925 mmol) and guanidine carbonate (3.12 g, 17.31 mmol) were dissolved in n-BuOH (31 mL) and MeONa (1.50 g, 27.70 mmol) was added. The mixture was heated at +125°C (oil bath temperature) for 20 hours. Saturated NH_4Cl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3x30 mL). Drying (Na_2SO_4), filtration and concentration gave a crude product which was purified by flash chromatography (CH_2Cl_2/MeOH 25:1 → 20:1 → 15:1) to afford a solid (1.3 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.24 (d, *J*=5.3 Hz, 1 H) 7.37 (s, 1 H) 6.83 (d, *J*=5.3 Hz, 1 H) 5.23 - 5.34 (m, 1 H) 5.04 (s, 2 H) 4.13 (dd, *J*=11.6, 4.5 Hz, 2 H) 3.44 - 3.54 (m, 2 H) 2.60 (s, 3 H) 2.43 - 2.56 (m, 2 H) 1.85 - 1.93 (m, 2 H); MS (ESI) *m/z* 260 (M + 1).

Example 40

***N*-{4-[(4-Methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**

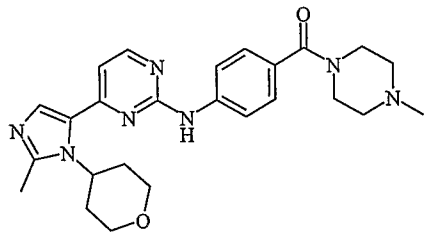


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (64.6 mg, 0.249 mmol, obtained Example 39(a)), 1-[(4-bromophenyl)sulfonyl]-4-methylpiperazine (described in WO 2003004472) (79.5 mg, 0.249 mmol), Cs_2CO_3 (162 mg, 0.498 mmol), $Pd_2(dba)_3$ (6 mg, 0.006 mmol) and X-Phos (7 mg, 0.013 mmol) to give the title compound (54 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.42 (d, *J*=5.3 Hz, 1 H) 7.89 (s, 1 H) 7.75 - 7.81 (m, 2 H) 7.65 (d, *J*=8.8 Hz, 2 H) 7.41 (s, 1 H) 7.00 (d, *J*=5.3 Hz, 1 H) 5.12 - 5.26 (m, 1 H) 4.05 (dd, *J*=11.6, 4.3 Hz, 2 H) 3.24 - 3.36 (m, 2 H) 3.02 (s, 4 H) 2.61 (s, 3 H) 2.37 - 2.53 (m, 6 H) 2.24 (s, 3 H) 1.85 (dd, *J*=12.1, 2.8 Hz, 2 H); MS (ESI) *m/z* 498 (M + 1).

Example 41

***N*-{4-[(4-Methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**

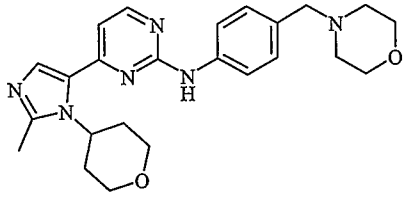


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (64.5 mg, 0.249 mmol, obtained Example 39(a)), 1-(4-bromobenzoyl)-4-methylpiperazine (described in WO 2003004472) (70.4 mg, 0.249 mmol), Cs_2CO_3 (162 mg, 0.497 mmol), $Pd_2(dba)_3$ (6 mg, 0.006 mmol) and X-Phos (7 mg, 0.012 mmol) to give the title compound (42 mg, 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38 (d, *J*=5.3 Hz, 1 H) 7.69 (s, 1 H) 7.62 (d, *J*=8.6 Hz, 2 H) 7.33 - 7.42 (m, 3 H) 6.94 (d, *J*=5.3 Hz, 1 H) 5.17 - 5.27 (m, 1 H) 4.01 (dd, *J*=11.5, 4.4 Hz, 2 H) 3.64 (s, 4 H) 3.16 - 3.32 (m, 2 H) 2.60 (s, 3 H) 2.33 - 2.53 (m, 6 H) 2.31 (s, 3 H) 1.84 (dd, *J*=12.3, 2.7 Hz, 2 H); MS (ESI) *m/z* 462 (M + 1).

Example 42

4-[2-Methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine

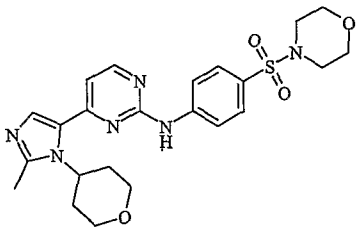


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (65.8 mg, 0.254 mmol, obtained Example 39(a)), 4-(4-bromobenzyl)morpholine (65.0 mg, 0.254 mmol), Cs_2CO_3 (165 mg, 0.508 mmol), $Pd_2(dba)_3$ (6 mg, 0.006 mmol) and X-Phos (7 mg, 0.013 mmol) to give the title compound (24 mg, 21%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.29 (d, *J*=5.3 Hz, 1 H) 7.42 (d, *J*=8.3 Hz, 2 H) 7.31 (s, 2 H) 7.19 (d, *J*=7.8 Hz, 2 H) 6.83 (d, *J*=5.3 Hz, 1 H) 5.16 - 5.28 (m, 1 H) 3.88 (dd, *J*=11.6, 4.3 Hz, 2 H) 3.59 - 3.68 (m, 4 H) 3.39 (s, 2 H) 3.03 - 3.14 (m, 2 H) 2.54 (s, 3 H) 2.35 - 2.42 (m, 4 H) 2.22 - 2.35 (m, 2 H) 1.76 (dd, *J*=12.3, 2.4 Hz, 2 H); MS (ESI) *m/z* 435 (M + 1).

Example 43

4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylsulfonyl)phenyl]pyrimidin-2-amine

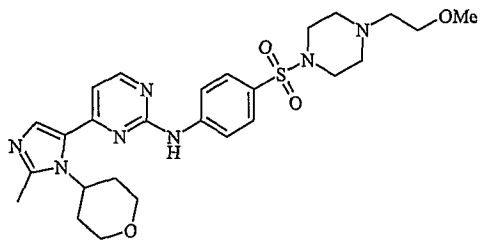


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (66.5 mg, 0.256 mmol, obtained Example 39(a)), 4-[(4-bromophenyl)sulfonyl]morpholine (78.5 mg, 0.256 mmol), Cs_2CO_3 (167 mg, 0.513 mmol), $Pd_2(dba)_3$ (6 mg, 0.006 mmol) and X-Phos (7 mg, 0.013 mmol) to give the title compound (30 mg, 24%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.44 (d, *J*=5.3 Hz, 1 H) 7.83 (d, *J*=8.8 Hz, 2 H) 7.69 (d, *J*=8.8 Hz, 2 H) 7.64 (s, 1 H) 7.45 (s, 1 H) 7.03 (d, *J*=5.3 Hz, 1 H) 5.10 - 5.24 (m, 1 H) 4.09 (dd, *J*=11.5, 4.4 Hz, 2 H) 3.69 - 3.80 (m, 4 H) 3.30 - 3.41 (m, 2 H) 2.94 - 3.07 (m, 4 H) 2.63 (s, 3 H) 2.44 - 2.59 (m, 2 H) 1.87 (dd, *J*=12.4, 2.8 Hz, 2 H); MS (ESI) *m/z* 485 (M + 1).

Example 44

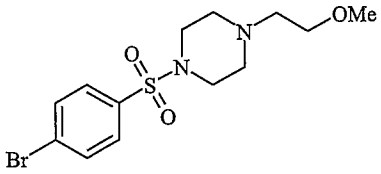
***N*-(4-{[4-(2-Methoxyethyl)piperazin-1-yl]sulfonyl}phenyl)-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**



The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (76.0 mg, 0.293 mmol, obtained from Example 39(a)), 1-[(4-bromophenyl)sulfonyl]-4-(2-methoxyethyl)piperazine (106.5 mg, 0.293 mmol, obtained from Example 44(a)), Cs_2CO_3 (191 mg, 0.586 mmol), $Pd_2(dba)_3$ (7 mg, 0.007 mmol) and X-Phos (9 mg, 0.015 mmol) to give the title compound (41 mg, 26%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.43 (d, *J*=5.3 Hz, 1 H) 7.78 (d, *J*=9.1 Hz, 3 H) 7.66 (d, *J*=8.8 Hz, 2 H) 7.42 (s, 1 H) 7.01 (d, *J*=5.3 Hz, 1 H) 5.14 - 5.25 (m, 1 H) 4.06 (dd, *J*=11.5, 4.4 Hz, 2 H) 3.43 (t, *J*=5.3 Hz, 2 H) 3.26 - 3.37 (m, 5 H) 3.05 (s, 4 H) 2.62 (s, 3 H) 2.55 (q, *J*=5.5 Hz, 6 H) 2.40 - 2.53 (m, 2 H) 1.86 (dd, *J*=12.3, 2.7 Hz, 2 H); MS (ESI) *m/z* 542 (M + 1).

Example 44(a) *1-[(4-Bromophenyl)sulfonyl]-4-(2-methoxyethyl)piperazine*

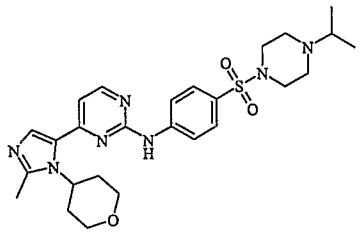


The title compound was prepared in accordance with the general method F using 4-bromobenzenesulfonyl chloride (201.7 mg, 0.789 mmol) and 1-(2-methoxyethyl)piperazine (113.8 mg, 0.789 mmol) to give the title compound (277 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64 - 7.69 (m, 2 H) 7.57 - 7.62 (m, 2 H) 3.47 (t, J=5.2 Hz, 2 H) 3.30 (s, 3 H) 3.08 (s, 4 H) 2.62 (d, J=4.8 Hz, 6 H); MS (ESI) m/z 364 (M + 1).

Example 45

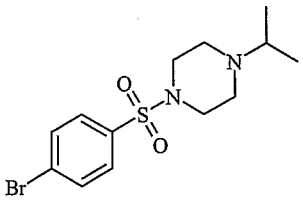
***N*-{4-[(4-Isopropylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**



The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (72.4 mg, 0.279 mmol, obtained from Example 39(a)), 1-[(4-bromophenyl)sulfonyl]-4-isopropylpiperazine (prepared as described in Example 45a) (97.0 mg, 0.279 mmol), Cs_2CO_3 (182.0 mg, 0.559 mmol), $Pd_2(dba)_3$ (6 mg, 0.007 mmol) and X-Phos (8 mg, 0.014 mmol) to give the title compound (35 mg, 24%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.43 (d, *J*=5.1 Hz, 1 H) 7.75 - 7.81 (m, 2 H) 7.72 (s, 1 H) 7.67 (d, *J*=8.6 Hz, 2 H) 7.43 (s, 1 H) 7.02 (d, *J*=5.1 Hz, 1 H) 5.14 - 5.25 (m, 1 H) 4.07 (dd, *J*=11.5, 4.4 Hz, 2 H) 3.27 - 3.38 (m, 2 H) 3.02 (s, 4 H) 2.64 - 2.71 (m, 1 H) 2.62 (s, 3 H) 2.55 - 2.61 (m, 4 H) 2.41 - 2.54 (m, 2 H) 1.86 (dd, *J*=12.4, 2.8 Hz, 2 H) 0.99 (d, *J*=6.6 Hz, 6 H); MS (ESI) *m/z* 526 (M + 1).

Example 45(a) *1-[(4-Bromophenyl)sulfonyl]-4-isopropylpiperazine*

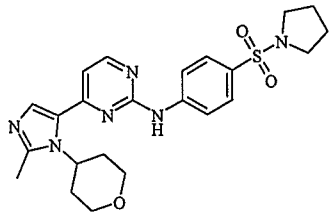


The title compound was prepared in accordance with the general method F using 4-bromobenzenesulfonyl chloride (272.5 mg, 1.067 mmol) and 1-isopropylpiperazine (136.7 mg, 1.067 mmol) to give the title compound (360 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64 - 7.70 (m, 2 H) 7.59 - 7.64 (m, 2 H) 3.02 (s, 4 H) 2.64 - 2.72 (m, 1 H) 2.55 - 2.63 (m, 4 H) 1.00 (d, *J*=6.6 Hz, 6 H); MS (ESI) *m/z* 348 (M + 1).

Example 46

4-[2-Methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine

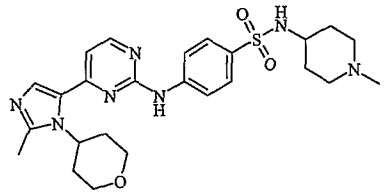


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (62.4 mg, 0.241 mmol, obtained from Example 39(a)), 1-[(4-bromophenyl)sulfonyl]pyrrolidine (69.8 mg, 0.241 mmol), Cs_2CO_3 (156.8 mg, 0.481 mmol), $Pd_2(dba)_3$ (6 mg, 0.006 mmol) and X-Phos (7 mg, 0.012 mmol) to give the title compound (58 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.43 (d, *J*=5.3 Hz, 1 H) 7.86 (s, 1 H) 7.72 - 7.81 (m, 4 H) 7.42 (s, 1 H) 7.00 (d, *J*=5.3 Hz, 1 H) 5.13 - 5.24 (m, 1 H) 4.05 (dd, *J*=11.5, 4.4 Hz, 2 H) 3.26 - 3.36 (m, 2 H) 3.18 - 3.26 (m, 4 H) 2.61 (s, 3 H) 2.40 - 2.53 (m, 2 H) 1.85 (dd, *J*=12.3, 2.7 Hz, 2 H) 1.70 - 1.78 (m, 4 H); MS (ESI) *m/z* 469 (M + 1).

Example 47

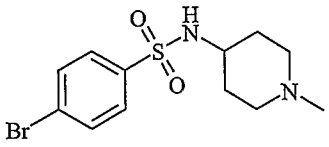
(*N*-(1-Methylpiperidin-4-yl)-4-({4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzenesulfonamide



The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (71.5 mg, 0.276 mmol, obtained from Example 39(a)), 4-bromo-*N*-(1-methylpiperidin-4-yl)benzenesulfonamide (obtained from Example 47(a)) (91.9 mg, 0.276 mmol), Cs_2CO_3 (179.7 mg, 0.552 mmol), $Pd_2(dba)_3$ (6 mg, 0.007 mmol) and X-Phos (8 mg, 0.014 mmol) to give the title compound (61 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.44 (d, *J*=5.3 Hz, 1 H) 7.81 (q, *J*=9.1 Hz, 4 H) 7.45 (s, 1 H) 7.04 (d, *J*=5.3 Hz, 1 H) 5.12 - 5.24 (m, 1 H) 4.10 (dd, *J*=11.6, 4.5 Hz, 2 H) 3.34 (t, *J*=11.1 Hz, 2 H) 3.00 (s, 2 H) 2.62 - 2.68 (m, 4 H) 2.53 (dd, *J*=12.6, 4.5 Hz, 4 H) 2.45 (s, 3 H) 2.02 (s, 3 H) 1.88 (dd, *J*=12.9, 3.3 Hz, 2 H) some overlap of protons; MS (ESI) *m/z* 512 (M + 1).

Example 47(a) *4-Bromo-N-(1-methylpiperidin-4-yl)benzenesulfonamide*

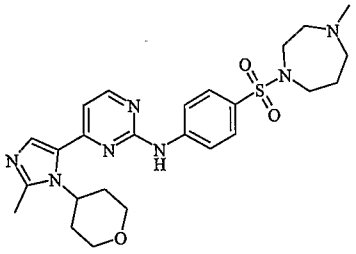


The title compound was prepared in accordance with the general method F using 4-bromobenzenesulfonyl chloride (200.5 mg, 0.785 mmol) and 1-methylpiperidin-4-amine (89.6 mg, 0.785 mmol) to give the title compound (245 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.72 - 7.78 (m, 2 H) 7.63 - 7.68 (m, 2 H) 3.11 - 3.22 (m, 1 H) 2.70 (d, *J*=11.6 Hz, 2 H) 2.24 (s, 3 H) 2.03 (t, *J*=10.9 Hz, 2 H) 1.73 - 1.83 (m, 2 H) 1.44 - 1.57 (m, 2 H); MS (ESI) *m/z* 334 (M + 1).

Example 48

***N*-{4-[(4-Methyl-1,4-diazepan-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**

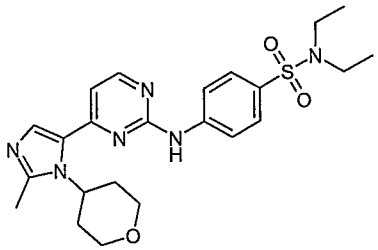


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine (53.0 mg, 0.204 mmol, obtained from Example 39(a)), 1-[(4-bromophenyl)sulfonyl]-4-methyl-1,4-diazepane (as described in WO 2003004472) (75.6 mg, 0.204 mmol), Cs_2CO_3 (199.8 mg, 0.613 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol) and X-Phos (6 mg, 0.010 mmol) to give the title compound (15 mg, 15%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.43 (d, *J*=5.3 Hz, 1 H) 7.69 - 7.81 (m, 4 H) 7.61 (s, 1 H) 7.44 (s, 1 H) 7.02 (d, *J*=5.3 Hz, 1 H) 5.12 - 5.24 (m, 1 H) 4.08 (dd, *J*=11.6, 4.5 Hz, 2 H) 3.27 - 3.46 (m, 6 H) 2.64 - 2.73 (m, 4 H) 2.63 (s, 3 H) 2.44 - 2.57 (m, 2 H) 2.38 (s, 3 H) 1.82 - 1.94 (m, 4 H); MS (ESI) *m/z* 512 (M + 1).

Example 49

***N,N*-Diethyl-4-({4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzenesulfonamide**

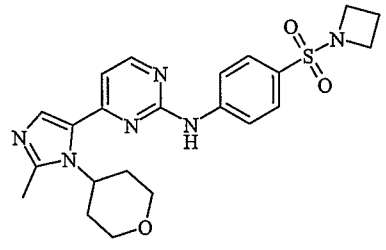


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine (54.9 mg, 0.212 mmol, obtained from Example 39(a)), 4-bromo-N,N-diethylbenzenesulfonamide (as described in *J. Med. Chem.*, 2000, **43**, 3878) (61.9 mg, 0.212 mmol), Cs_2CO_3 (138.0 mg, 0.423 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol) and X-Phos (6 mg, 0.011 mmol) to give the title compound (69 mg, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.41 (d, *J*=5.3 Hz, 1 H) 7.96 (s, 1 H) 7.67 - 7.77 (m, 4 H) 7.40 (s, 1 H) 6.99 (d, *J*=5.1 Hz, 1 H) 5.13 - 5.24 (m, 1 H) 4.02 (dd, *J*=11.5, 4.4 Hz, 2 H) 3.24 - 3.33 (m, 2 H) 3.21 (q, *J*=7.2 Hz, 4 H) 2.60 (s, 3 H) 2.36 - 2.51 (m, 2 H) 1.84 (dd, *J*=12.4, 2.8 Hz, 2 H) 1.11 (t, *J*=7.2 Hz, 6 H); MS (ESI) *m/z* 471 (M + 1).

Example 50

***N*-[4-(Azetidin-1-ylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**

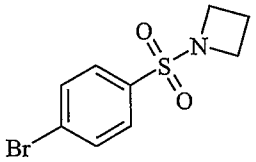


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (59.2 mg, 0.228 mmol, obtained from Example 39(a)), 1-[(4-bromophenyl)sulfonyl]azetidine (obtained from Example 50(a)) (63.0 mg, 0.228 mmol), Cs_2CO_3 (148.8 mg, 0.457 mmol),

$Pd_2(dba)_3$ (5 mg, 0.006 mmol) and X-Phos (7 mg, 0.011 mmol) to give the title compound (28 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.45 (d, *J*=5.3 Hz, 1 H) 7.81 - 7.88 (m, 2 H) 7.74 - 7.81 (m, 3 H) 7.44 (s, 1 H) 7.03 (d, *J*=5.3 Hz, 1 H) 5.13 - 5.25 (m, 1 H) 4.08 (dd, *J*=11.6, 4.5 Hz, 2 H) 3.77 (t, *J*=7.7 Hz, 4 H) 3.28 - 3.39 (m, 2 H) 2.63 (s, 3 H) 2.43 - 2.57 (m, 2 H) 2.02 - 2.11 (m, 2 H) 1.87 (dd, *J*=12.4, 2.8 Hz, 2 H); MS (ESI) *m/z* 455 (M + 1).

Example 50(a) *1-[(4-Bromophenyl)sulfonyl]azetidine*

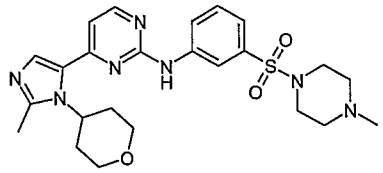


The title compound was prepared in accordance with the general method F using 4-bromobenzenesulfonyl chloride (314.4 mg, 1.230 mmol) and azetidine (70.3 mg, 1.230 mmol) to give the title compound (315 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.72 (d, *J*=1.5 Hz, 4 H) 3.80 (t, 4 H) 2.06 - 2.17 (m, 2 H); MS (ESI) *m/z* 277 (M + 1).

Example 51

***N*-{3-[(4-Methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**

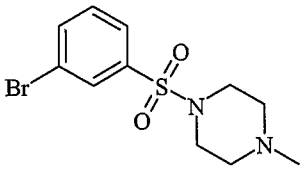


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (60.1 mg, 0.232 mmol, obtained from Example 39(a)), 1-[(3-bromophenyl)sulfonyl]-4-methylpiperazine (obtained from Example 51a) (74.0 mg, 0.232 mmol), Cs_2CO_3 (151.0 mg, 0.464 mmol), $Pd_2(dba)_3$ (5 mg, 0.006 mmol) and X-Phos (7 mg, 0.012 mmol) to give the title compound (65 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38 (d, *J*=5.3 Hz, 1 H) 8.00 (s, 1 H) 7.96 (s, 1 H) 7.86 (d, *J*=8.6 Hz, 1 H) 7.34 - 7.46 (m, 3 H) 6.95 (d, *J*=5.3 Hz, 1 H) 5.12 - 5.24 (m, 1 H) 3.99

(dd, *J*=11.5, 4.2 Hz, 2 H) 3.20 (t, *J*=11.2 Hz, 2 H) 3.03 (s, 4 H) 2.59 (s, 3 H) 2.30 - 2.48 (m, 6 H) 2.22 (s, 3 H) 1.84 (dd, *J*=12.1, 2.5 Hz, 2 H); MS (ESI) *m/z* 498 (M + 1).

Example 51(a) *1-[(3-Bromophenyl)sulfonyl]-4-methylpiperazine*

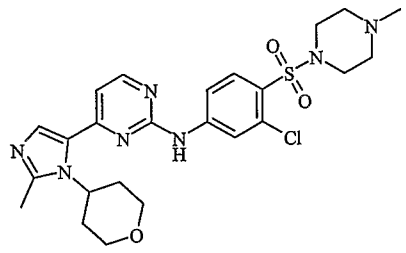


The title compound was prepared in accordance with the general method F using 3-bromobenzenesulfonyl chloride (357.1 mg, 1.398 mmol) and 1-methylpiperazine (153.9 mg, 1.537 mmol) to give the title compound (393 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (t, *J*=1.8 Hz, 1 H) 7.71 - 7.75 (m, 1 H) 7.66 - 7.70 (m, 1 H) 7.41 (t, *J*=8.0 Hz, 1 H) 3.06 (s, 4 H) 2.45 - 2.53 (m, 4 H) 2.28 (s, 3 H); MS (ESI) *m/z* 320 (M + 1).

Example 52

***N*-{3-Chloro-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**

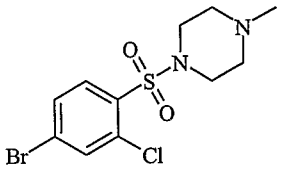


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (59.0 mg, 0.228 mmol, obtained from Example 39(a)), 1-[(4-bromo-2-chlorophenyl)sulfonyl]-4-methylpiperazine (obtained from Example 52(a)) (80.5 mg, 0.228 mmol), Cs_2CO_3 (148.3 mg, 0.455 mmol), $Pd_2(dba)_3$ (5 mg, 0.006 mmol) and X-Phos (7 mg, 0.011 mmol) to give the title compound (59 mg, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.43 (d, *J*=5.3 Hz, 1 H) 8.05 (s, 1 H) 8.00 (d, *J*=2.3 Hz, 1 H) 7.90 (d, *J*=8.8 Hz, 1 H) 7.50 (dd, *J*=8.7, 2.1 Hz, 1 H) 7.42 (s, 1 H) 7.03 (d, *J*=5.3 Hz, 1 H) 5.12 - 5.24 (m, 1 H) 4.05 (dd, *J*=11.5, 4.4 Hz, 2 H) 3.22 - 3.35 (m, 6 H) 2.61 (s, 3 H)

2.37 - 2.52 (m, 6 H) 2.26 (s, 3 H) 1.87 (dd, *J*=12.4, 2.8 Hz, 2 H); MS (ESI) *m/z* 533 (M + 1).

Example 52(a) *1-[(4-Bromo-2-chlorophenyl)sulfonyl]-4-methylpiperazine*

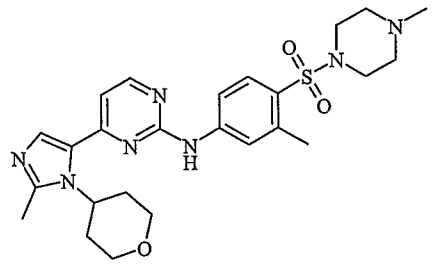


The title compound was prepared in accordance with the general method F using 4-bromo-2-chlorobenzenesulfonyl chloride (326.0 mg, 1.124 mmol) and 1-methylpiperazine (123.9 mg, 1.234 mmol) to give the title compound (406 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.86 (d, *J*=8.6 Hz, 1 H) 7.67 (d, *J*=1.8 Hz, 1 H) 7.51 (dd, *J*=8.6, 2.0 Hz, 1 H) 3.26 - 3.34 (m, 4 H) 2.42 - 2.49 (m, 4 H) 2.29 (s, 3 H); MS (ESI) *m/z* 354 (M + 1).

Example 53

***N*-{3-Methyl-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**

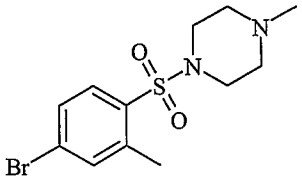


The title compound was prepared in accordance with the general method E using 4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (60.1 mg, 0.232 mmol, obtained from Example 39(a)), 1-[(4-bromo-2-methylphenyl)sulfonyl]-4-methylpiperazine (obtained from Example 53(a)) (77.2 mg, 0.232 mmol), Cs_2CO_3 (151.0 mg, 0.463 mmol), $Pd_2(dba)_3$ (5 mg, 0.006 mmol) and X-Phos (7 mg, 0.012 mmol) to give the title compound (49 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.42 (d, *J*=5.3 Hz, 1 H) 7.81 (d, *J*=8.6 Hz, 1 H) 7.63 - 7.70 (m, 2 H) 7.46 (d, *J*=2.0 Hz, 1 H) 7.42 (s, 1 H) 6.99 (d, *J*=5.3 Hz, 1 H) 5.13 - 5.25 (m, 1 H) 4.05 (dd, *J*=11.6, 4.3 Hz, 2 H) 3.24 - 3.35 (m, 2 H) 3.11 - 3.22 (m, 4 H) 2.60 (d, *J*=7.6

Hz, 6 H) 2.38 - 2.53 (m, 6 H) 2.27 (s, 3 H) 1.84 (dd, *J*=12.3, 2.7 Hz, 2 H); MS (ESI) *m/z* 512 (M + 1).

Example 53(a) *1-[(4-Bromo-2-methylphenyl)sulfonyl]-4-methylpiperazine*

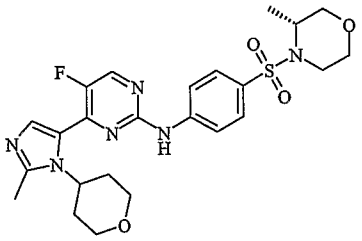


The title compound was prepared in accordance with the general method F using 4-bromo-2-methylbenzenesulfonyl chloride (332.6 mg, 1.234 mmol) and 1-methylpiperazine (135.9 mg, 1.357 mmol) to give the title compound (411 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (d, *J*=8.3 Hz, 1 H) 7.44 - 7.52 (m, 2 H) 3.23 (s, 4 H) 2.61 (s, 3 H) 2.49 (s, 4 H) 2.32 (s, 3 H); MS (ESI) *m/z* 334 (M + 1).

Example 54

5-Fluoro-*N*-(4-{[(3*R*)-3-methylmorpholin-4-yl]sulfonyl}phenyl)-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine

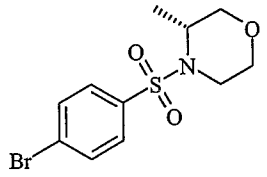


The title compound was prepared in accordance with the general method E using 5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (52.0 mg, 0.188 mmol, obtained from Example 7(e)), (3*R*)-4-[(4-bromophenyl)sulfonyl]-3-methylmorpholine (obtained from Example 54(a)) (60.0 mg, 0.188 mmol), Cs_2CO_3 (122.2 mg, 0.375 mmol), $Pd_2(dba)_3$ (4 mg, 0.005 mmol) and X-Phos (7 mg, 0.009 mmol) to give the title compound (24 mg, 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.36 (d, *J*=3.0 Hz, 1 H) 7.70 - 7.77 (m, 5 H) 7.68 (d, *J*=3.8 Hz, 1 H) 4.99 - 5.12 (m, 1 H) 4.10 (dd, *J*=11.7, 4.7 Hz, 2 H) 3.92 (q, *J*=6.7 Hz, 1 H) 3.78 - 3.85 (m, 1 H) 3.54 - 3.63 (m, 2 H) 3.40 - 3.52 (m, 2 H) 3.34 (t, *J*=11.6 Hz, 2 H) 3.21

- 3.30 (m, 1 H) 2.65 (s, 3 H) 2.48 - 2.62 (m, 2 H) 1.87 (dd, *J*=12.8, 3.7 Hz, 2 H) 1.17 (d, *J*=6.8 Hz, 3 H); MS (ESI) *m/z* 517 (M + 1).

Example 54(a) *(3R)-4-[(4-Bromophenyl)sulfonyl]-3-methylmorpholine*

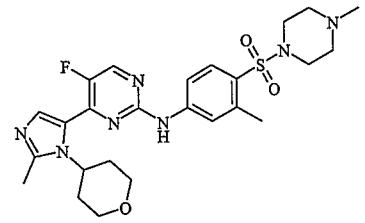


The title compound was prepared in accordance with the general method F using 4-bromobenzenesulfonyl chloride (294.9 mg, 1.154 mmol) and (3*R*)-3-methylmorpholine (128.4 mg, 1.269 mmol) to give the title compound (368 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.67 (d, *J*=2.3 Hz, 4 H) 3.80 - 3.86 (m, 1 H) 3.58 (d, *J*=2.3 Hz, 2 H) 3.42 - 3.50 (m, 2 H) 3.21 - 3.30 (m, 1 H) 1.45 (d, *J*=6.6 Hz, 1 H) 1.15 (d, *J*=6.8 Hz, 3 H); MS (ESI) *m/z* 321 (M + 1).

Example 55

5-Fluoro-*N*-{3-methyl-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine



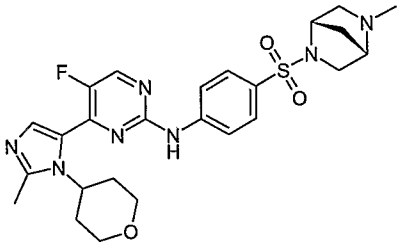
The title compound was prepared in accordance with the general method E using 5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (54.6 mg, 0.202 mmol, obtained from Example 7(e)), 1-[(4-bromo-2-methylphenyl)sulfonyl]-4-methylpiperazine (obtained from Example 53(a)) (67.3 mg, 0.202 mmol), Cs_2CO_3 (131.6 mg, 0.404 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol) and X-Phos (6 mg, 0.010 mmol) to give the title compound (46 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.34 (d, *J*=2.8 Hz, 1 H) 7.81 (d, *J*=8.6 Hz, 1 H) 7.65 (d, *J*=3.8 Hz, 1 H) 7.57 - 7.63 (m, 2 H) 7.42 (d, *J*=2.0 Hz, 1 H) 5.03 - 5.14 (m, 1 H) 4.07 (dd, *J*=11.6, 4.5 Hz, 2 H) 3.26 - 3.37 (m, 2 H) 3.11 - 3.23 (m, 4 H) 2.63 (s, 3 H) 2.59 (s, 3

H) 2.39 - 2.57 (m, 6 H) 2.27 (s, 3 H) 1.85 (dd, *J*=12.1, 3.0 Hz, 2 H); MS (ESI) *m/z* 530 (M + 1).

Example 56

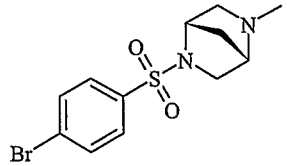
5-Fluoro-*N*-(4-{[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]sulfonyl}phenyl)-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine



The title compound was prepared in accordance with the general method E using 5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (53.3 mg, 0.197 mmol, obtained from Example 7(e)), (1*S*,4*S*)-2-[(4-bromophenyl)sulfonyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane (obtained from Example 56(a)) (65.3 mg, 0.197 mmol), Cs_2CO_3 (128.5 mg, 0.394 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol) and X-Phos (6 mg, 0.010 mmol) to give the title compound (60 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.34 (d, *J*=2.8 Hz, 1 H) 7.88 (s, 1 H) 7.73 (s, 4 H) 7.64 (d, *J*=3.8 Hz, 1 H) 5.00 - 5.12 (m, 1 H) 4.22 (s, 1 H) 4.06 (dd, *J*=11.6, 4.5 Hz, 2 H) 3.53 (d, *J*=9.9 Hz, 1 H) 3.27 - 3.37 (m, 3 H) 3.00 (dd, *J*=9.6, 2.3 Hz, 1 H) 2.83 (dd, *J*=9.9, 2.5 Hz, 1 H) 2.65 (s, 1 H) 2.62 (s, 3 H) 2.43 - 2.57 (m, 2 H) 2.33 (s, 3 H) 1.85 (dd, *J*=12.5, 3.4 Hz, 2 H) 1.67 (d, *J*=9.9 Hz, 1 H) 1.12 (d, *J*=10.1 Hz, 1 H); MS (ESI) *m/z* 528 (M + 1).

Example 56(a) (1S,4S)-2-[(4-Bromophenyl)sulfonyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane



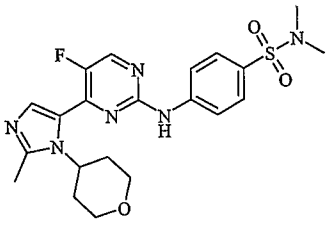
The title compound was prepared in accordance with the general method F using 4-bromobenzenesulfonyl chloride (309.0 mg, 1.209 mmol), (1*S*,4*S*)-2-methyl-2,5-

diazabicyclo[2.2.1]heptane hydrobromide (364.5 mg, 1.330 mmol) and also adding Et_3N (367.1 mg, 3.628 mmol) to give the title compound (400 mg, 100%).

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.65 - 7.73 (m, 4 H) 4.27 (s, 1 H) 3.56 (dd, *J*=9.6, 1.3 Hz, 1 H) 3.36 (s, 1 H) 3.02 (dd, *J*=9.6, 2.3 Hz, 1 H) 2.86 (dd, *J*=9.9, 2.5 Hz, 1 H) 2.65 (dd, *J*=10.0, 1.1 Hz, 1 H) 2.36 (s, 3 H) 1.74 (d, *J*=9.9 Hz, 1 H) 1.17 (d, *J*=9.9 Hz, 1 H); MS (ESI) *m/z* 332 (M + 1).

Example 57

4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide

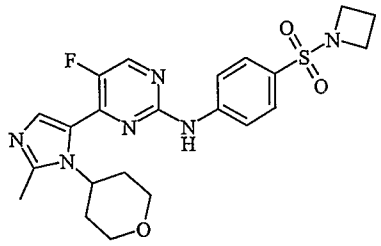


The title compound was prepared in accordance with the general method E using 5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (54.1 mg, 0.200 mmol, obtained from Example 7(e)), 4-bromo-*N*,*N*-dimethylbenzenesulfonamide (52.9 mg, 0.200 mmol), Cs_2CO_3 (130.4 mg, 0.400 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol) and X-Phos (6 mg, 0.010 mmol) to give the title compound (44 mg, 47%).

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.35 (d, *J*=2.8 Hz, 1 H) 7.82 (s, 1 H) 7.73 - 7.78 (m, 2 H) 7.67 - 7.71 (m, 2 H) 7.65 (d, *J*=3.8 Hz, 1 H) 5.03 - 5.13 (m, 1 H) 4.07 (dd, *J*=11.6, 4.5 Hz, 2 H) 3.28 - 3.38 (m, 2 H) 2.69 (s, 6 H) 2.64 (s, 3 H) 2.44 - 2.58 (m, 2 H) 1.86 (dd, *J*=12.1, 3.0 Hz, 2 H); MS (ESI) *m/z* 461 (M + 1).

Example 58

***N*-[4-(Azetidin-1-ylsulfonyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**

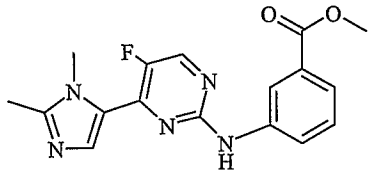


The title compound was prepared in accordance with the general method E using 5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (54.3 mg, 0.201 mmol, obtained from Example 7(e)), 1-[(4-bromophenyl)sulfonyl]azetidine (55.5 mg, 0.201 mmol, obtained from Example 50(a)), Cs_2CO_3 (130.9 mg, 0.402 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol) and X-Phos (6 mg, 0.010 mmol) to give the title compound (38 mg, 40%).

1H NMR (400 MHz, $CDCl_3$) δ ppm 8.36 (d, *J*=3.0 Hz, 1 H) 7.85 (s, 1 H) 7.73 - 7.83 (m, 4 H) 7.66 (d, *J*=3.8 Hz, 1 H) 5.00 - 5.17 (m, 1 H) 4.08 (dd, *J*=11.6, 4.8 Hz, 2 H) 3.76 (t, *J*=7.7 Hz, 4 H) 3.28 - 3.40 (m, 2 H) 2.64 (s, 3 H) 2.44 - 2.59 (m, 2 H) 2.01 - 2.13 (m, 2 H) 1.87 (dd, *J*=12.3, 3.2 Hz, 2 H); MS (ESI) *m/z* 473 (M + 1).

Example 59

Methyl 3-{[4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}benzoate



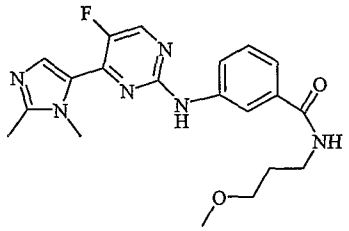
2-Chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (49 mg, 0.22 mmol, 1.0 equiv., obtained from Example 1(b)), methyl-3-aminobenzoate (38 mg, 0.25 mmol, 1.15 equiv.) and Cs_2CO_3 (0.11 g, 0.33 mmol, 1.5 equiv.) were mixed in 1,4-dioxane (2 mL) and the mixture was flushed with argon for 10 minutes. $Pd_2(dba)_3$ (11mg, 0.012.mmol, 054 equiv.) and X-Phos (11 mg, 0.022 mmol,.0.10 equiv.) were added and the reaction mixture was flushed with argon for another 10 minutes before the reaction was stirred for 16 h at +90 °C under an atmosphere of Argon. The reaction mixture was diluted with CH_2Cl_2, filtered and evaporated. The residue was taken up in CH_2Cl_2 and the organic phase was washed with H_2O. Residual water was removed from the organic phase by addition of absolute EtOH before evaporation. The crude of the product was purified by flash

chromatography (gradient from 100 % CH_2Cl_2 to 5 % MeOH in CH_2Cl_2) to yield a solid (48 mg, 60%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.81 (s, 1 H) 8.54 (d, 1 H) 8.34 (t, 1 H) 7.92 (dd, 1 H) 7.59 - 7.52 (m, 2 H) 7.43 (t, 1 H) 3.93 (s, 3 H) 3.85 (s, 3 H) 2.41 (s, 3 H); MS (ESI) *m/z* 340 (M-1).

Example 60

3-[[4-(2,3-Dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-N-(3-methoxypropyl)benzamide hydrochloride

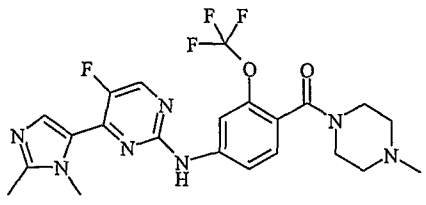


The title compound was prepared in accordance with the general method G using flash chromatography (gradient from 100 % EtOAc to 5 % MeOH in EtOAc) for purification. Using methyl 3-{[4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}benzoate (44.5 mg, 0.13 mmol, obtained from Example 59), $Al(CH_3)_3$ (94 mg, 1.3 mmol, 2.0 M in toluene) and 3-methoxypropan-1-amine (68.9 mg, 0.78 mmol), the base of the title compound (26 mg, 46%) was obtained as a solid. The hydrochloride was prepared in accordance with the method described within general method D.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.97 (s, 1 H) 8.76 (d, 1 H) 8.45 - 8.38 (m, 1 H) 8.19 (d, 1 H) 8.13 (t, 1 H) 7.83 - 7.76 (m, 1 H) 7.47 (d, 1 H) 7.39 (t, 1 H) 4.02 (s, 3 H) 3.39 - 3.29 (m, 4 H) 3.24 (s, 3 H) 2.67 (s, 3 H) 1.80 - 1.71 (m, 2 H); MS (ESI) *m/z* 399 (M+1).

Example 61

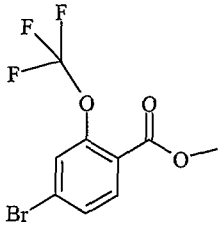
[4-[[4-(2,3-Dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-2-(trifluoromethoxy)phenyl]-(4-methylpiperazin-1-yl)methanone hydrochloride



The title compound was prepared in accordance with the general method G using flash chromatography (gradient from 100 % dichloromethane to 10 % MeOH in dichloromethane) for purification. Using methyl 4-{[4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}-2-(trifluoromethoxy)benzoate (obtained from Example 61(b)) (33 mg, 0.078 mmol), $Al(CH_3)_3$ (56 mg, 0.78 mmol, 2.0 M in toluene) and 1-methylpiperazine (47 mg, 0.47 mmol), the base of the title compound (18 mg, 40%) was obtained as a solid. The hydrochloride was prepared in accordance with th method described within general method D.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.34 (s, 1 H) 8.82 (d, 1 H) 8.16 (d, 1 H) 7.91 (s, 1 H) 7.83 (dd, 1 H) 7.49 (d, 1 H) 4.03 (s, 3 H) 3.09 - 2.87 (m, 4 H) 2.80 (s, 3 H) 2.66 (s, 3 H); MS (ESI) *m/z* 493 (M+1).

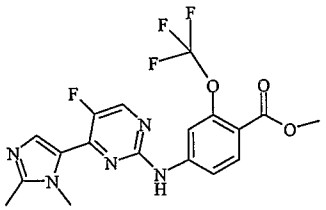
Example 61(a) *Methyl 4-bromo-2-(trifluoromethoxy)benzoate*



4-Bromo-1-iodo-2-(trifluoromethoxy)benzene (0.340 g, 0.93 mmol), $Pd(OAc)_2$ (0.011 g, 0.049 mmol), dppp (0.020 g, 0.048 mmol) and triethylamine (0.218 g, 2.15 mmol) were suspended in MeOH (10 mL) in a 300 mL glass vessel. The vessel was evacuated and filled with nitrogen gas (repeated 3 times) followed by evacuation and filling with CO gas (repeated 2 times) to establish a homogenous CO gas atmosphere at ~3.5 bar. Heating in an oil bath at +65 °C for 90 minutes resulted in ~50 % conversion of the start material as juged by GCMS. After addition of more $Pd(OAc)_2$ (0.009 g, 0.040 mmol), dppp (0.018 g, 0.044 mmol) and triethylamine (0.58 g, 0.57 mmol) CO gas atmosphere was established as described above and the reaction was continued at +65 °C for another 130 minutes. When the mixture was cool (r.t) it was filtrered through diatomaceous earth and the solvent was evaporated. The crude product was purified by flash chromatography (gradient from 100 % heptane to 20 % EtOAc in heptane) to give the title compound as a clear liquid (0.068 g, 24.5%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.92 - 7.85 (m, 1 H) 7.84-7.76 (m, 2 H) 3.85 (s, 3 H); MS (CI) *m/z* 299 (^{79}Br) (M+1).

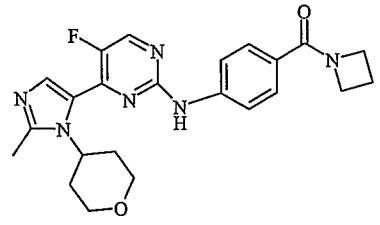
Example 61(b) Methyl 4-{[4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}-2-(trifluoromethoxy)benzoate



The title compound was prepared in accordance with the general method E (workup procedure A) with the exception that purification of the crude product was done by flash chromatography (gradient from 100 % heptane to 100 % EtOAc). Using 4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine (obtained from Example 25(a)) (38 mg, 0.18 mmol), methyl 4-bromo-2-(trifluoromethoxy)benzoate (obtained from Example 61(a)) (64 mg, 0.21 mmol), Cs_2CO_3 (90 mg, 0.28 mmol), $Pd_2(dba)_3$ (8 mg, 0.009 mmol) and X-Phos (8 mg, 0.017 mmol), the title compound (33 mg, 42%) was obtained as a solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.25 (s, 1 H) 8.63 (d, 1 H) 7.98-7.82 (m, 3 H) 7.58 (d, 1 H) 3.95 (s, 3 H) 3.81 (s, 3 H) 2.42 (s, 3 H); MS (ESI) *m/z* 426 (M+1).

Example 62

N-[4-(Azetidin-1-ylcarbonyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride



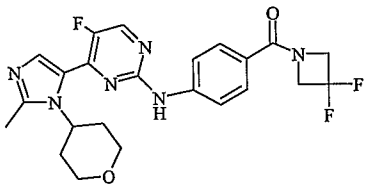
The title compound was prepared in accordance with the general method E (Workup procedure C), with the exception that the base of the product was purified by flash chromatography (gradient from 100 % DCM to 5 % MeOH in DCM). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (53 mg, 0.19 mmol), 1-(4-chlorobenzoyl)azetidine (*J. Org. Chem.*, 1974,

39(13), 1973) (39 mg, 0.20 mmol), Cs_2CO_3 (95 mg, 0.29 mmol), $Pd_2(dba)_3$ (8 mg, 0.009 mmol) and X-Phos (10 mg, 0.02 mmol), the base of the title compound (52 mg, 62%) was obtained as a solid. The hydrochloride was prepared in accordance with the method described in general method D.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.09 (s, 1 H) 8.81 (d, 1 H) 8.02 (s, 1 H) 7.69 (d, 2 H) 7.56 (d, 2 H) 5.05 - 4.90 (m, 1 H) 4.40 - 4.18 (m, 2 H) 4.12 - 3.91 (m, 2 H) 3.81 (dd, 2 H) 3.16 (t, 2 H) 2.78 (s, 3 H) 2.30 - 2.07 (m, 4 H) 1.92 (dd, 2 H); MS (ESI) *m/z* 437 (M+1).

Example 63

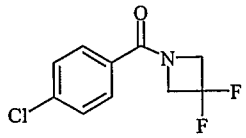
N-{4-[(3,3-Difluoroazetidin-1-yl)carbonyl]phenyl}-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride



The title compound was prepared in accordance with the general method E (Workup procedure C), with the exception that the base of the product was purified by flash chromatography (gradient from 100 % CH_2Cl_2 to 5 % MeOH in CH_2Cl_2). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (49 mg, 0.18 mmol), 1-(4-chlorobenzoyl)-3,3-difluoroazetidine (44 mg, 0.19 mmol), Cs_2CO_3 (104 mg, 0.32 mmol), $Pd_2(dba)_3$ (9 mg, 0.010 mmol) and X-Phos (10 mg, 0.02 mmol), the base of the title compound (68 mg, 64%) was obtained as a solid. The hydrochloride was prepared in accordance with the general method D.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.15 (s, 1 H) 8.83 (d, 1 H) 8.02 (s, 1 H) 7.74 (d, 2 H) 7.63 (d, 2 H) 5.03 - 4.91 (m, 1 H) 5.0 – 4.2 (m, 4 H) 3.82 (dd, 2 H) 3.18 (t, 2 H) 2.78 (s, 3 H) 2.24 - 2.08 (m, 2 H) 1.99 - 1.85 (m, 2 H); MS (ESI) *m/z* 473 (M+1).

Example 63(a) *4-Bromo-2-(trifluoromethoxy)benzoic acid*

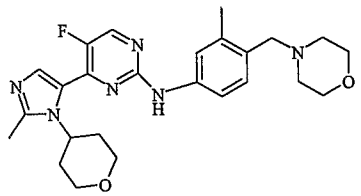


Thionyl chloride (5 mL) was added to 4-chloro-benzoic acid (0.49 g, 3.1 mmol). After addition of 2 drops of anhydrous DMF, the reaction mixture was refluxed for ~15 minutes under an atmosphere of nitrogen. The solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (5 mL). 3,3-difluoroazetidine hydrochloride (0.42 g, 3.3 mmol)) was added followed by addition of triethylamine (0.91 mL, 6.6 mmol). The reaction mixture was stirred at r.t. for ~15 minutes before it was diluted with CH_2Cl_2, washed with i) saturated $NaHCO_3$ (aq.) and ii) water. To the organic phase Abs. (absolute) EtOH was added (until a clear solution was obtained) and the solvents were evaporated *in vacuo* to give the title compound as a solid in 94 % yield. The isolated material was used in the next step without further purification.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.75 - 7.66 (m, 2 H) 7.58 - 7.48 (m, 2 H) 5.06 - 4.15 (m, 4 H); MS (ESI) *m/z* 232 (M+1).

Example 64

5-Fluoro-N-[3-methyl-4-(morpholin-4-ylmethyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride

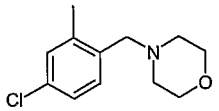


The title compound was prepared in accordance with the general method E (Workup procedure C), with the exception that the base of the product was purified by flash chromatography (gradient from 100 % CH_2Cl_2 to 6 % MeOH in CH_2Cl_2) before final purification by preparative HPLC. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (70 mg, 0.25 mmol), 4-(4-chloro-2-methylbenzyl)morpholine (obtained from Example 64(a)) (60 mg, 0.27 mmol), Cs_2CO_3 (136 mg, 0.42 mmol), $Pd_2(dba)_3$ (13 mg, 0.014 mmol) and X-Phos (15 mg, 0.031 mmol), the base of the title compound was prepared and transformed into the hydrochloride in accordance with the method described within general method D to yield (67 mg, 53%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.54 (br s, 1 H) 9.90 (s, 1 H) 8.79 (d, 1 H) 8.00 (s, 1 H) 7.63 - 7.50 (m, 2 H) 7.48 (d, 1 H) 5.05 - 4.90 (m, 1 H) 4.27 (br. s., 2 H) 3.98 - 3.75

(m, 6 H) 3.11 - 3.24 (m, 6 H, partly obscured by HDO signal) 2.78 (s, 3 H) 2.38 (s, 3 H) 2.24 - 2.07 (m, 2 H) 1.92 (dd, 2 H); MS (ESI) *m/z* 465 (M-1).

Example 64(a) *4-(4-Chloro-2-methylbenzyl)morpholine*

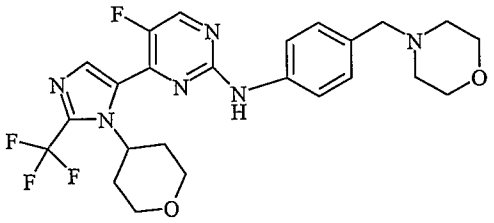


To a stirred, cooled (0 °C) solution of 4-chloro-2-methylbenzaldehyde (0.23 g, 1.5 mmol) in MeOH (5 mL) was added morpholine (0.15 g, 1.7 mmol), $NaCNBH_3$ (0.49 g, 7.8 mmol) and HOAc (0.063 g, 1.0 mmol) and the reaction was stirred at r.t. over night. The solvent was removed *in vacuo* and the crude product was partitioned between EtOAc / 1M $NaHCO_3$ (aq.). The organic phase was dried (Na_2SO_4), filtered, concentrated and purified twice by flash chromatography (gradient from 100% pentane to 10% EtOAc in pentane) to give the title compound as a clear liquid (0.120 g, 35%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.27 - 7.21 (m, 2 H) 7.20 - 7.14 (m, 1 H) 3.57 - 3.49 (m, 4 H) 3.38 (s, 2 H) 2.36 - 2.31 (m, 4 H) 2.31 (s, 3 H); MS (ESI) *m/z* 226 (M+1).

Example 65

5-Fluoro-N-[4-(morpholin-4-ylmethyl)phenyl]-4-[3-oxan-4-yl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-amine hydrochloride

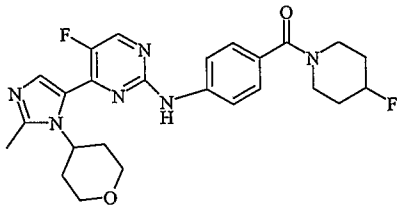


The title compound was prepared in accordance with the general method E and work-up procedure B. The product was purified by flash chromatography (CH_2Cl_2/MeOH 20:1). Using 5-Fluoro-4-[1-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 34(d)) (38 mg, 0.115 mmol), 4-(4-bromobenzyl)-morpholine (0.028 g, 0.11 mmol), Cs_2CO_3 (75 mg, 0.23 mmol), $Pd_2(dba)_3$ (8 mg, 0.0086 mmol) and X-Phos (8.2 mg, 0.017 mmol), the base of the title compound (42 mg, 76%) was obtained as a solid. The hydrochloride was prepared in accordance with the method described in general method D.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1 H), 8.73 (d, 1 H), 7.55-7.53 (m, 3 H), 7.21 (d, 2 H), 4.81 (m, 1 H), 3.78 (m, 2 H), 3.55 (t, 4 H), 3.39 (s, 2 H), 3.18 (t, 2 H), 2.32 (m, 4 H), 2.13 (m, 2 H), 1.86 (m, 2 H); MS (ES) m/z 505 (M-1).

Example 66

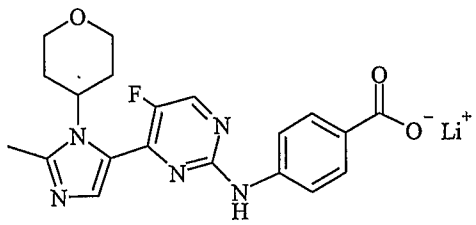
5-Fluoro-N-{4-[(4-fluoropiperidin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride



To a solution of lithium 4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzoate (obtained from Example 66(a)) (50 mg, 0.12 mmol) in anhydrous DMF (0.5 mL) was added a solution of HBTU (56 mg, 0.15 mmol) in DMF (0.5 mL) and the mixture was shaken for 1h at r.t.. 4-Fluoropiperidine hydrochloride (22 mg, 0.16 mmol) was then added followed by the addition of DIPEA (65 mg, 0.50 mmol) and the reaction mixture was shaken o.n. (over night) at r.t. The crude of the base product was purified using preparative HPLC and was transferred into the hydrochloride in accordance with the method described within general method D to yield the title compound (37 mg, 54%) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.02 (s, 1 H) 8.80 (d, 1 H) 8.02 (s, 1 H) 7.66 (d, 2 H) 7.35 (d, 2 H) 4.79 - 5.04 (m, 2 H) 3.81 (dd, 2 H) 3.57 (br.s., 2 H) 3.14 (t, 2 H) 2.78 (s, 3 H) 2.23 - 2.07 (m, 2 H) 1.99 - 1.79 (m, 4 H) 1.71 (br.s., 2 H); MS (ESI) *m/z* 483 (M+1).

Example 66(a) Lithium 4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzoate

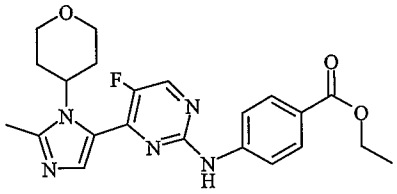


Ethyl 4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzoate (obtained from Example 67) (1.16 g, 2.73 mmol) and LiOH x H_2O (115 mg, 2.74 mmol) were slurried in EtOH (15 mL) and H_2O (4.4 mL). The slurry was heated at +50-60°C under an atmosphere of Argon for 20 h then the reaction mixture was allowed to stand for 6 days at r.t.. The solvents were then evaporated and the residue was slurried in THF / H_2O 9:1 and heated at +60°C for 24 h. No more conversion of the ester was seen (LCMS). LiOH x H_2O (59 mg, 1.16 mmol) was added in two portions and the slurry was heated at +60°C for ~20 h. Removal of the solvents *in vacuo* gave the title compound as a solid (1.17 g). The isolated material was used in amidation reactions without further purification.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (s, 1 H) 8.54 (d, 1 H) 7.75 (d, 2 H) 7.45 (d, 2 H) 7.32 (d, 1 H) 5.11 - 4.98 (m, 1 H) 3.78 (dd, 2 H) 3.05 (t, 2 H) 2.53 (s, 3 H) 2.24 - 2.08 (m, 2 H) 1.78 (dd, 2 H); MS (ESI) *m/z* 398 (M+1).

Example 67

Ethyl 4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzoate

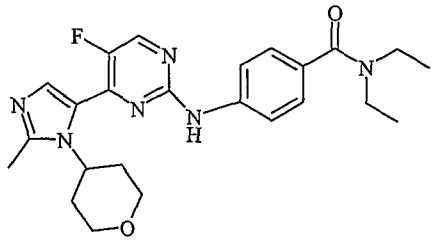


The title compound was prepared in accordance with the general method E (Workup procedure C), with the exception that the base of the product was purified by flash chromatography (gradient from 100 % CH_2Cl_2 to 5 % MeOH in CH_2Cl_2). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (794 mg, 2.86 mmol), ethyl 4-iodobenzoate (820 mg, 2.97 mmol), Cs_2CO_3 (1.48 g, 4.54 mmol), $Pd_2(dba)_3$ (59 mg, 0.064 mmol) and X-Phos (63 mg, 0.13 mmol), the title compound (1.16 g, 95%) was obtained as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.97 (s, 1 H) 8.64 (d, 1 H) 7.86 (d, 2 H) 7.76 (d, 2 H) 7.35 (d, 1 H) 5.08 - 4.96 (m, 1 H) 4.27 (q, 2 H) 3.81 (dd, 2 H) 3.12 (t, 2 H) 2.54 (s, 3 H) 2.27 - 2.11 (m, 2 H) 1.82 (dd, 2 H) 1.30 (t, 3 H); MS (ESI) *m/z* 426 (M+1).

Example 68

***N,N*-Diethyl-4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzamide hydrochloride**

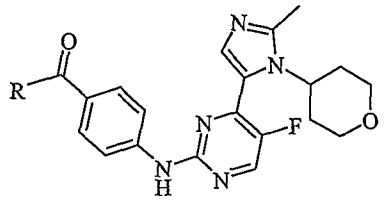


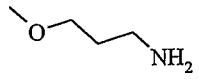
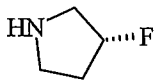
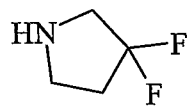
To a solution of lithium 4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzoate (obtained from Example 66(a)) (50 mg, 0.12 mmol) in anhydrous DMF (0.5 mL) was added a solution of HBTU (56 mg, 0.15 mmol) in DMF (0.5 mL) and the mixture was shaken for 1h at r.t.. Diethyl amine (13 mg, 0.18 mmol) was then added followed by the addition of DIPEA (48 mg, 0.37 mmol) and the reaction mixture was shaken over night. at r.t.. The crude of the base product was purified using preparative HPLC and was transferred into the hydrochloride in accordance with the method described in the general method D to yield the title compound (34 mg, 56%) as a solid.

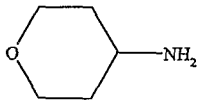
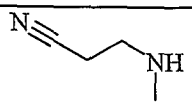
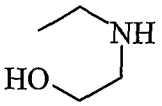
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 (s, 1 H) 8.81 (d, 1 H) 8.03 (s, 1 H) 7.66 (d, 2 H) 7.29 (d, 2 H) 5.05-4.92 (m, 1 H) 3.82 (dd, 2 H) 3.16 (t, 3 H) 2.78 (s, 3 H) 2.24-2.08 (m, 2 H) 1.97-1.86 (m, 2 H) 1.10 (t, 6 H); MS (ESI) *m/z* 453 (M+1).

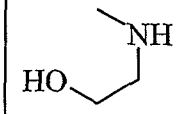
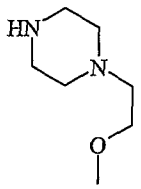
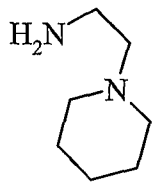
Examples 69-91

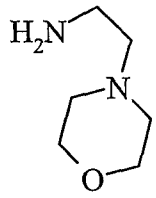
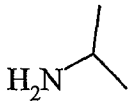
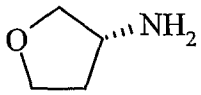
The following Examples were prepared according to the procedure described in Examples 66 and 68 except that the quantity of DIPEA used in each case was adjusted depending on whether the starting amine was a free base, mono- or higher salt. 3 equivalents of DIPEA were used for amines that were freebases and one additional equivalent was added for every additional salt. The group R is an amine connected *via* the nitrogen to form an amide.

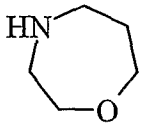
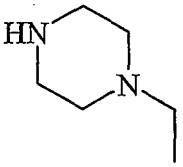
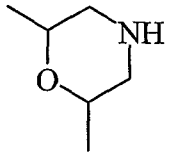
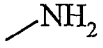


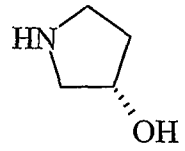
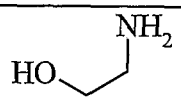
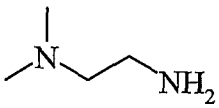
Ex	R	NMR	Yield	M/z
69		^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.78 (s, 1 H) 8.61 (d, 1 H) 8.26 (t, 1 H) 7.80 - 7.72 (m, 2 H) 7.70 - 7.63 (m, 2 H) 7.34 (d, 1 H) 5.08 - 4.97 (m, 1 H) 3.81 (dd, 2 H) 3.23 (s, 3 H) 3.08 (t, 2 H) 2.54 (s, 3 H) 2.25 - 2.11 (m, 2 H) 1.80 (dd, 2 H) 1.78 - 1.69 (m, 2 H)	67%	469
70		9.80 (s, 1 H) 8.61 (d, 1 H) 7.68 (d, 2 H) 7.55 - 7.43 (m, 2 H) 7.34 (d, 1 H) 5.33 (dd, 1 H) 5.08 - 4.94 (m, 1 H) 3.90 - 3.50 (m, 6-7 H uncertain integral) 3.17 - 3.04 (m, 2 H) 2.54 (s, 3 H) 2.25 – 1.95 (m, 4 H) 1.86 - 1.75 (m, 2 H)	67%	469
71		9.82 (s, 1 H) 8.61 (d, 1 H) 7.70 (d, 2 H) 7.50 (d, 2 H) 7.34 (d, 1 H) 5.07 - 4.94 (m, 1 H) 3.89 (t, 2 H) 3.82 (dd, 2 H) 3.71 (t, 2 H) 3.11 (t, 2 H) 2.54 (s, 3 H) 2.5 - 2.37 (m, 2 H) 2.24 - 2.11 (m, 2 H) 1.81 (dd, 2 H)	73%	487

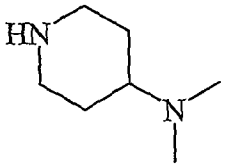
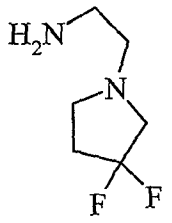
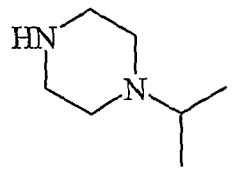
Ex	R	NMR	Yield	M/z
72		9.78 (s, 1 H) 8.61 (d, 1 H) 8.08 (d, 1 H) 7.81 - 7.75 (m, 2 H) 7.71 - 7.64 (m, 2 H) 7.34 (d, 1 H) 5.07 - 4.95 (m, 1 H) 4.04 - 3.92 (m, 1 H) 3.91 - 3.84 (m, 2 H) 3.81 (dd, 2 H) 3.10 (t, 2 H) 2.54 (s, 3 H) 2.25 - 2.11 (m, 2 H) 1.86 - 1.69 (m, 4 H) 1.63 - 1.50 (m, 2 H). 27 of 29 signals reported, signals obscured by HDO	48%	481
73		9.78 (s, 1 H) 8.60 (d, 1 H) 7.68 (d, 2 H) 7.38 - 7.30 (m, 3 H) 5.07 - 4.95 (m, 1 H) 3.82 (dd, 2 H) 3.63 (br. s., 2 H) 3.11 (t, 2 H) 2.84 (t, 2 H) 2.53 (s, 3 H) 2.24 - 2.11 (m, 2 H) 1.80 (dd, 2 H)	55%	464
74		9.72 (s, 1 H) 8.59 (d, 1 H) 7.64 (d, 2 H) 7.33 (d, 1 H) 7.30 (d, 2 H) 5.06 - 4.94 (m, 1 H) 4.75 (t, 1 H) 3.83 (dd, 2 H) 3.53 (br. s., 2 H) 3.11 (t, 2 H) 2.53 (s, 3 H) 2.24 - 2.10 (m, 2 H) 1.80 (dd, 2 H) 1.15 - 1.00 (m, 3 H)	33%	469

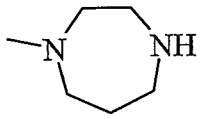
Ex	R	NMR	Yield	M/z
75		9.74 (s, 1 H) 8.60 (d, 1 H) 7.64 (d, 2 H) 7.39 - 7.28 (m, 3 H) 5.07 - 4.94 (m, 1 H) 4.81 - 4.71 (m, 1 H) 3.82 (dd, 2 H) 3.54 (br. s., 2 H) 3.11 (t, 2 H) 2.96 (s, 3 H) 2.54 (s, 3 H) 2.24 - 2.10 (m, 2 H) 1.80 (dd, 2 H)	35%	455
76		9.76 (s, 1 H) 8.59 (d, 1 H) 7.69 - 7.63 (m, 2 H) 7.36 - 7.28 (m, 3 H) 5.06 - 4.94 (m, 1 H) 3.81 (dd, 2 H) 3.55 - 3.40 (m, 6 H uncertain integral) 3.22 (s, 3 H) 3.09 (t, 2 H) 2.53 (s, 3 H) 2.42 (br. s., 3 H uncertain integral) 2.24 - 2.10 (m, 2 H) 1.79 (dd, 2 H)	64%	524
77		9.79 (s, 1 H) 8.61 (d, 1 H) 8.23 - 8.12 (m, 1 H) 7.79 - 7.71 (m, 2 H) 7.70 - 7.64 (m, 2 H) 7.34 (d, 1 H) 5.08 - 4.97 (m, 1 H) 3.81 (dd, 2 H) 3.08 (t, 2 H) 2.54 (s, 3 H) 2.38 (br s, 4 H uncertain integral) 2.24 - 2.11 (m, 2 H) 1.80 (dd, 2 H) 1.55 - 1.43 (m, 4 H) 1.42 - 1.31 (m, 2 H)	73%	508

Ex	R	NMR	Yield	M/z
78		9.80 (s, 1 H) 8.61 (d, 1 H) 8.24 - 8.14 (m, 1 H) 7.79 - 7.71 (m, 2 H) 7.70 - 7.63 (m, 2 H) 7.34 (d, 1 H) 5.08 - 4.97 (m, 1 H) 3.81 (dd, 2 H) 3.62 - 3.51 (m, 4 H) 3.07 (t, 2 H) 2.54 (s, 3 H) 2.5 - 2.34 (m, 6 H uncertain integral) 2.24 - 2.11 (m, 2 H) 1.80 (dd, 2 H)	56%	510
79		9.76 (s, 1 H) 8.61 (d, 1 H) 7.99 (d, 1 H) 7.77 (d, 2 H) 7.66 (d, 2 H) 7.35 (d, 1 H) 5.07 - 4.95 (m, 1 H) 4.14 - 4.01 (m, 1 H) 3.81 (dd, 2 H) 3.10 (t, 2 H) 2.54 (s, 3 H) 2.25 - 2.10 (m, 2 H) 1.80 (dd, 2 H) 1.15 (d, 6 H)	51%	439
80		9.79 (s, 1 H) 8.61 (d, 1 H) 8.30 (d, 1 H) 7.79 (d, 2 H) 7.68 (d, 2 H) 7.34 (d, 1 H) 5.07 - 4.95 (m, 1 H) 4.48 - 4.39 (m, 1 H) 3.89 - 3.76 (m, 4 H) 3.74 - 3.66 (m, 1 H) 3.56 (dd, 1 H) 3.10 (t, 2 H) 2.54 (s, 3 H) 2.25 - 2.08 (m, 3 H) 1.95 - 1.85 (m, 1 H) 1.80 (dd, 2 H)	51%	467

Ex	R	NMR	Yield	M/z
81		9.74 (s, 1 H) 8.60 (d, 1 H) 7.66 (d, 2 H) 7.37 - 7.26 (m, 3 H) 5.07 - 4.94 (m, 1 H) 3.82 (dd, 2 H) 3.78 - 3.55 (m, 6 H) 3.50 (br.s., 2 H) 3.10 (t, 2 H) 2.53 (s, 3 H) 2.24 - 2.10 (m, 2 H) 1.80 (dd, 2 H) 1.91 - 1.67 (m, 2 H)	68%	481
82		9.76 (s, 1 H) 8.59 (d, 1 H) 7.66 (d, 2 H) 7.36 - 7.27 (m, 3 H) 5.06 - 4.94 (m, 1 H) 3.81 (dd, 2 H) 3.47 (m, 4 H) 3.09 (t, 2 H) 2.53 (s, 3 H) 2.43 - 2.26 (m, 6 H) 2.24 - 2.10 (m, 2 H) 1.79 (dd, 2 H) 0.99 (t, 3 H)	68%	494
83		9.78 (s, 1 H) 8.60 (d, 1 H) 7.67 (d, 2 H) 7.38 - 7.27 (m, 3 H) 5.07 - 4.96 (m, 1 H) 3.81 (dd, 2 H) 3.57 - 3.47 (m, 2 H) 3.08 (t, 2 H) 2.53 (s, 3 H) 2.24 - 2.10 (m, 2 H) 1.79 (dd, 2 H) 1.06 (br. s., 6 H)	44%	495
84		9.79 (s, 1 H) 8.61 (d, 1 H) 8.23 (q, 1 H) 7.78 - 7.72 (m, 2 H) 7.69 - 7.64 (m, 2 H) 7.34 (d, 1 H) 5.08 - 4.96 (m, 1 H) 3.81 (dd, 2 H) 3.08 (t, 2 H) [2.76 (s, 1.5 H) 2.75 (s, 1.5 H)] rot. 2.54 (s, 3 H) 2.24 - 2.11 (m, 2 H) 1.80 (dd, 2 H)	23%	411

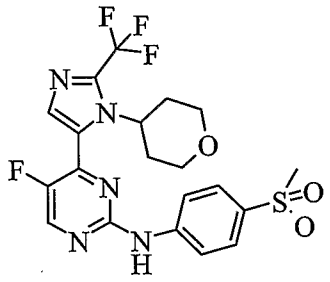
Ex	R	NMR	Yield	M/z
85		9.77 (s, 1 H) 8.60 (d, 1 H) 7.66 (d, 2 H) 7.50 - 7.40 (m, 2 H) 7.33 (d, 1 H) 5.07 - 4.95 (m, 1 H) 4.95 (dd, 1 H) 4.35 - 4.18 (m, 1 H) 3.88 - 3.76 (m, 2 H) 3.65 – 3.20 (multiplets partly obscured by HDO-signal, no reliable integral) 3.11 (t, 2 H) 2.54 (s, 3 H) 2.25 - 2.10 (m, 2 H) 1.99 - 1.72 (m, 4 H)	36%	467
86		9.79 (s, 1 H) 8.61 (d, 1 H) 8.24 (t, 1 H) 7.81 - 7.75 (m, 2 H) 7.71 - 7.65 (m, 2 H) 7.35 (d, 1 H) 5.07 - 4.96 (m, 1 H) 4.70 (t, 1 H) 3.82 (dd, 2 H) 3.53 - 3.45 (m, 3 H) 3.10 (t, 2 H) 2.54 (s, 3 H) 2.25 - 2.11 (m, 2 H) 1.81 (dd, 2 H)	53%	441
87		9.79 (s, 1 H) 8.61 (d, 1 H) 8.19 (t, 1 H) 7.79 - 7.72 (m, 2 H) 7.70 - 7.64 (m, 2 H) 7.34 (d, 1 H) 5.08 - 4.96 (m, 1 H) 3.81 (dd, 2 H) 3.09 (t, 2 H) 2.54 (s, 3 H) 2.47 – 2.38 (m, 2 H) 2.26 - 2.11 (m, 8 H) 1.80 (dd, 2 H)	60%	468

Ex	R	NMR	Yield	M/z
88		9.75 (s, 1 H) 8.59 (d, 1 H) 7.65 (d, 2 H) 7.38 - 7.25 (m, 3 H) 5.07 - 4.94 (m, 1 H) 3.81 (dd, 2 H) 3.09 (t, 2 H) 2.90 (br. s., 2 H) 2.53 (s, 3 H) 2.30 - 2.09 (m, 8 H) 1.86 - 1.67 (m, 4 H) 1.43 - 1.26 (m, 2 H)	67%	508
89	 Described in WO 2005097750	9.80 (s, 1 H) 8.61 (d, 1 H) 8.27 (t, 1 H) 7.80 - 7.72 (m, 2 H) 7.71 - 7.64 (m, 2 H) 7.35 (d, 1 H) 5.07 - 4.97 (m, 1 H) 3.81 (dd, 2 H) 3.08 (t, 2 H) 2.93 (t, 2 H) 2.73 (t, 2 H) 2.59 (t, 2 H) 2.54 (s, 3 H) 2.27 - 2.10 (m, 4 H) 1.80 (dd, 2 H)	71%	530
90		9.76 (s, 1 H) 8.60 (d, 1 H) 7.66 (d, 2 H) 7.36 - 7.27 (m, 3 H) 5.06 - 4.94 (m, 1 H) 3.81 (dd, 2 H) 3.45 (br s not possible to integrate) 3.09 (t, 2 H) 2.53 (s, 3 H) 2.42 (br. s., 4 H) 2.24 - 2.10 (m, 2 H) 1.79 (dd, 2 H) 0.97 (s, 3 H) 0.96 (s, 3 H). Two broad overlapping signals could not be integrated accurately	65%	508

Ex	R	NMR	Yield	M/z
91		9.73 (s, 1 H) 8.59 (d, 1 H) 7.65 (d, 2 H) 7.33 (d, 1 H) 7.3 (d, 2 H) 5.06 - 4.95 (m, 1 H) 3.81 (dd, 2 H) 3.58 (br. s., 2 H) 3.43 (br. s., 2 H uncertain integral) 3.09 (t, 2 H) 2.63 (br. s., 1 H uncertain integral) 2.53 (s, 3 H) 2.33 - 2.10 (m, 5 H) 1.88 - 1.69 (m, 4 H)	66%	494

Example 92

5-Fluoro-*N*-[4-(methylsulfonyl)phenyl]-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine

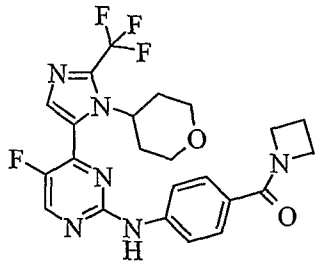


The title compound was prepared in accordance with the general method E using 5-fluoro-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (66 mg, 0.2 mmol, obtained from Example 34(d)) and 4-bromophenyl methyl sulfone (47 mg, 0.2 mmol) to give the title compound (43 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.46 (d, *J*=2.27 Hz, 1 H) 7.76 - 7.87 (m, 4 H) 7.63 (d, *J*=3.03 Hz, 1 H) 4.72 - 4.85 (m, 1 H) 4.04 (dd, *J*=11.87, 4.80 Hz, 2 H) 3.37 - 3.49 (m, 2 H) 3.02 (s, 3 H) 2.56 - 2.73 (m, 2 H); MS (ESI) *m/z* 486 (M + 1).

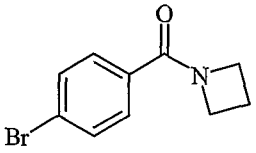
Example 93

***N*-[4-(Azetidin-1-ylcarbonyl)phenyl]-5-fluoro-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**



The title compound was prepared in accordance with the general method E using 5-fluoro-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (66 mg, 0.2 mmol, obtained from Example 34(d)) and 1-(4-bromobenzoyl)azetidine (obtained from 93(a)) (48 mg, 0.2 mmol) to give the title compound (48 mg, 49%).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.46 (d, *J*=2.53 Hz, 1 H) 7.71 (d, *J*=3.03 Hz, 1 H) 7.57 - 7.69 (m, 4 H) 4.80 - 4.92 (m, 1 H) 4.30 (d, *J*=44.21 Hz, 4 H) 4.08 (dd, *J*=11.62, 4.80 Hz, 2 H) 2.64 - 2.79 (m, 2 H) 2.30 - 2.44 (m, 2 H) 1.86 (d, *J*=8.84 Hz, 2 H); MS (ESI) *m/z* 491 (M + 1).

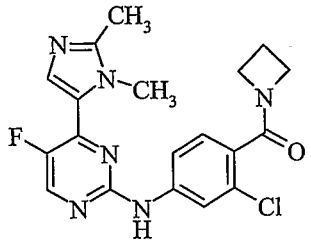
Example 93(a) *1-(4-Bromobenzoyl)azetidine*



Azetidine (275 mg, 4.82 mmol) followed by Et_3N (0.66 mL, 4.8 mmol) was added dropwise to 4-bromobenzoyl chloride (1.0 g, 4.56 mmol) in DCM (10 mL). The mixture was stirred 30 min before it was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ (aq.), water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (heptan to Heptan: EtOAc 1:4) to give the title compound (765 mg, 70%) as a solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.47 - 7.58 (m, 4 H) 4.26 (t, *J*=7.83 Hz, 4 H) 2.29 - 2.43 (m, 2 H); MS (ESI) *m/z* 240 (M + 1).

Example 94

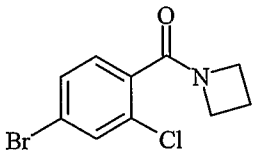
***N*-[4-(Azetidin-1-ylcarbonyl)-3-chlorophenyl]-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine**



The title compound was prepared in accordance with the general method E using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (26 mg, 0.125 mmol, obtained from Example 25(a)) and 1-(4-bromo-2-chlorobenzoyl)azetidine (obtained from Example 94(a)) (35 mg, 0.127 mmol) to give the title compound (17 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.46 (d, *J*=2.53 Hz, 1 H) 7.71 (d, *J*=3.03 Hz, 1 H) 7.57 - 7.69 (m, 4 H) 4.80 - 4.92 (m, 1 H) 4.30 (d, *J*=44.21 Hz, 4 H) 4.08 (dd, *J*=11.62, 4.80 Hz, 2 H) 3.42 (t, *J*=12.00 Hz, 2 H) 2.64 - 2.79 (m, 2 H) 2.30 - 2.44 (m, 2 H) 1.86 (d, *J*=8.84 Hz, 2 H); MS (ESI) *m/z* 491 (M + 1).

Example 94(a) *1-(4-Bromo-2-chlorobenzoyl)azetidine*

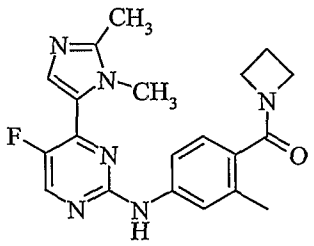


The title compound was prepared in accordance with the general method H using 4-bromo-2-chlorobenzoic acid (0.75 g, 3.19 mmol) and azetidine (192 mg, 3.36 mmol) to give the title compound (800 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.58 (d, *J*=2.02 Hz, 1 H) 7.45 (dd, *J*=8.08, 1.77 Hz, 1 H) 7.22 (d, *J*=8.08 Hz, 1 H) 4.22 (t, *J*=7.83 Hz, 2 H) 3.97 (t, 2 H) 2.28 - 2.41 (m, 2 H); MS (ESI) *m/z* 274 (M + 1).

Example 95

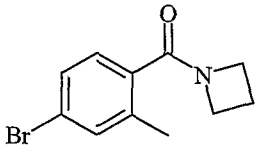
***N*-[4-(Azetidin-1-ylcarbonyl)-3-methylphenyl]-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine**



The title compound was prepared in accordance with the general method E using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (30 mg, 0.145 mmol, obtained from Example 25(a)) and 1-(4-bromo-2-methylbenzoyl)azetidine (obtained from Example 95(a)) (37 mg, 0.145 mmol) to give the title compound (32 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.27 (d, *J*=3.03 Hz, 1 H) 7.75 (d, *J*=4.29 Hz, 1 H) 7.36 - 7.45 (m, 2 H) 7.18 - 7.26 (m, 2 H) 4.21 (t, *J*=7.58 Hz, 2 H) 3.98 (t, *J*=7.58 Hz, 2 H) 3.93 (s, 3 H) 2.48 (s, 3 H) 2.25 - 2.36 (m, 2 H); MS (ESI) *m/z* 381 (M + 1).

Example 95(a) *1-(4-Bromo-2-methylbenzoyl)azetidine*

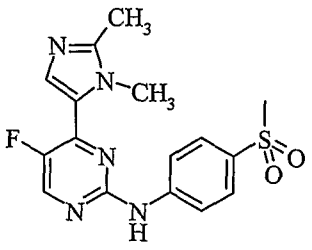


The title compound was prepared in accordance with the general method H using 4-bromo-2-methylbenzoic acid (1.0 g, 3.93 mmol) and azetidine (225 mg, 3.94 mmol) to give the title compound (670 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38 - 7.41 (m, 1 H) 7.33 (dd, *J*=8.08, 1.52 Hz, 1 H) 7.11 (d, *J*=8.08 Hz, 1 H) 4.06 (d, *J*=97.01 Hz, 4 H) 2.38 (s, 3 H) 2.27 - 2.36 (m, 2 H); MS (ESI) *m/z* 254 (M + 1).

Example 96

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(methylsulfonyl)phenyl]pyrimidin-2-amine

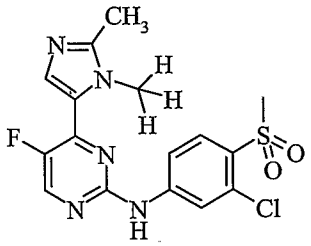


The title compound was prepared in accordance with the general method E using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (40 mg, 0.193 mmol, obtained from Example 25(a)) and 4-bromophenyl methyl sulfone (47 mg, 0.20 mmol) to give the title compound (21 mg, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.32 (d, *J*=3.03 Hz, 1 H) 7.84 - 7.91 (m, 2 H) 7.75 - 7.82 (m, 3 H) 7.70 (s, 1 H) 3.95 (s, 3 H) 3.06 (s, 3 H) 2.50 (s, 3 H); MS (ESI) *m/z* 362 (M + 1).

Example 97

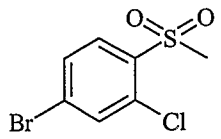
N-[3-Chloro-4-(methylsulfonyl)phenyl]-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine



The title compound was prepared in accordance with the general method E using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (40 mg, 0.193 mmol, obtained from Example 25(a)) and 4-bromo-2-chlorophenyl methyl sulfone (obtained from 97(a)) (54 mg, 0.20 mmol) to give the title compound (21 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.34 (d, *J*=3.03 Hz, 1 H) 8.10 (d, *J*=2.02 Hz, 1 H) 8.03 (d, *J*=8.84 Hz, 1 H) 7.85 (s, 1 H) 7.79 (d, *J*=4.55 Hz, 1 H) 7.49 (dd, *J*=8.72, 2.15 Hz, 1 H) 3.98 (s, 3 H) 3.27 (s, 3 H) 2.51 (s, 3 H); MS (ESI) *m/z* 396 (M+ 1).

Example 97(a) *4-Bromo-2-chlorophenyl methyl sulfone*



4-Bromo-2-chlorobenzenesulfonyl chloride (960 mg, 3.3 mmol) was added in portion to a solution of Na_2SO_3 (460 mg, 3.6 mmol) and $NaHCO_3$ (555 mg, 6.6 mmol) in H_2O (5 mL) at +75 °C. After 2 h. at +75 °C the reaction mixture was allowed to reach r.t. and MeI (1 mL, 16 mmol) was added. The mixture was heated in a microwave oven (+100 °C, 2 min).

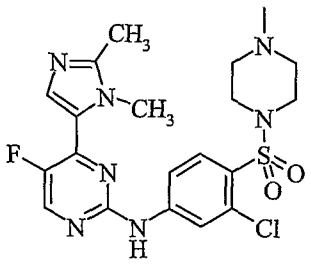
The reaction mixture was cooled to r.t. and diluted with CH_2Cl_2. The organic phase was washed with H_2O, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound (450 mg, 50 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.02 (d, *J*=8.59 Hz, 1 H) 7.75 (d, *J*=1.77 Hz, 1 H) 7.64 (dd, *J*=8.59, 1.77 Hz, 1 H) 3.27 (s, 3 H);

MS (ESI) *m/z* 268 (M^+).

Example 98

***N*-{3-Chloro-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine**

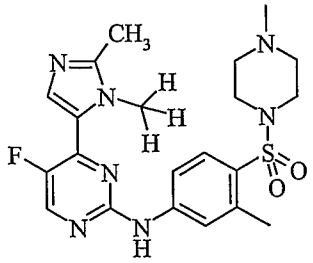


The title compound was prepared in accordance with the general method E using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (40 mg, 0.193 mmol, obtained from Example 25(a)) and 1-[(4-bromo-2-chlorophenyl)sulfonyl]-4-methylpiperazine (obtained from example 52(a)) (70 mg, 0.198 mmol) to give the title compound (29 mg, 31%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.34 (d, *J*=3.03 Hz, 1 H) 8.05 (d, *J*=2.02 Hz, 1 H) 7.95 (d, *J*=8.84 Hz, 1 H) 7.80 (d, *J*=4.55 Hz, 1 H) 7.49 (s, 1 H) 7.43 (dd, *J*=8.84, 2.27 Hz, 1 H) 3.99 (s, 3 H) 3.26 - 3.35 (m, 4 H) 2.52 (s, 3 H) 2.44 - 2.49 (m, 4 H) 2.30 (s, 3 H); MS (ESI) *m/z* 480 (M+ 1).

Example 99

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{3-methyl-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine

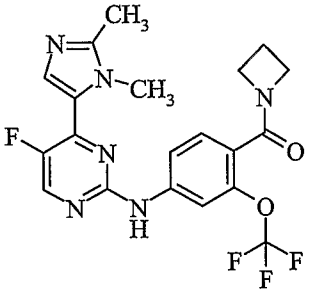


The title compound was prepared in accordance with the general method E using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (40 mg, 0.193 mmol, obtained from Example 25(a)) and 1-[(4-bromo-2-methylphenyl)sulfonyl]-4-methylpiperazine (obtained from Example 53(a)) (66 mg, 0.198 mmol) to give the title compound (32 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.34 (d, *J*=3.03 Hz, 1 H) 8.05 (d, *J*=2.02 Hz, 1 H) 7.95 (d, *J*=8.84 Hz, 1 H) 7.80 (d, *J*=4.55 Hz, 1 H) 7.49 (s, 1 H) 7.43 (dd, *J*=8.84, 2.27 Hz, 1 H) 3.99 (s, 3 H) 3.26 - 3.37 (m, 4 H) 2.52 (s, 3 H) 2.44 - 2.50 (m, 4 H) 2.30 (s, 3 H); MS (ESI) *m/z* 460 (M + 1).

Example 100

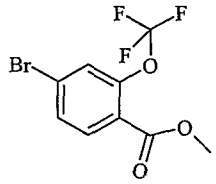
***N*-[4-(Azetidin-1-ylcarbonyl)-3-(trifluoromethoxy)phenyl]-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine**



The title compound was prepared in accordance with the general method E using 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine (40 mg, 0.193 mmol, obtained from Example 25(a)) and 1-[4-bromo-2-(trifluoromethoxy)benzoyl]azetidine (obtained from Example 100(c)) (64 mg, 0.197 mmol) to give the title compound (29 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.31 (d, *J*=3.03 Hz, 1 H) 7.72 - 7.79 (m, 2 H) 7.65 (s, 1 H) 7.45 (d, *J*=1.01 Hz, 2 H) 4.21 (t, *J*=7.71 Hz, 2 H) 4.05 (t, *J*=7.71 Hz, 2 H) 2.49 (s, 3 H) 2.27 - 2.37 (m, 2 H); MS (ESI) *m/z* 451 (M + 1).

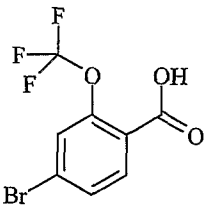
Example 100(a) *Methyl 4-bromo-2-(trifluoromethoxy)benzoate*



To 4-bromo-1-iodo-2-(trifluoromethoxy)benzene (2.0 g, 5.45 mmol), $Pd(OAc)_2$ (121 mg, 0.54 mmol), dppp (222 mg, 0.54 mmol) and Et_3N (2.3 mL, 16.3 mmol) in MeOH (50 mL) was introduced CO (g) to a pressure of 2.5 bar. The mixture was stirred at 2.5 bar and at +65 °C for 4h. The mixture was filtered through diatomaceous earth and the residue was concentrated *in vacuo*. The crude product was purified by flash chromatography (Heptan to Heptane:EtOAc 4: 1) to give the title compound (900 mg, 55%) as a liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.86 (d, *J*=8.34 Hz, 1 H) 7.55 (dd, *J*=8.46, 1.89 Hz, 1 H) 7.50 - 7.53 (m, 1 H) 3.94 (s, 3 H); MS (ESI) *m/z* 298 (M^+).

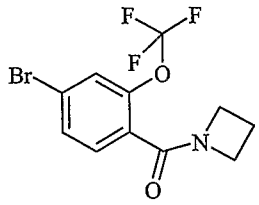
Example 100(b) *4-Bromo-2-(trifluoromethoxy)benzoic acid*



LiOH monohydrate (75 mg, 1.79 mmol) was added to methyl 4-bromo-2-(trifluoromethoxy)benzoate (400 mg, 1.34 mmol, obtained from 100(a)) in THF: H_2O (9:1, 5 mL). The mixture was heated in a microwave oven (+120 °C, 10 min). The reaction mixture was cooled to r.t. and diluted with CH_2Cl_2 and H_2O. 2 M HCl was added until pH 1. The mixture was extracted and the water phase was re-extracted with CH_2Cl_2. The organic phases were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound (300 mg, 79 %) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.99 (d, *J*=8.34 Hz, 1 H) 7.59 (dd, *J*=8.34, 1.77 Hz, 1 H) 7.55 - 7.57 (m, *J*=1.26 Hz, 1 H); MS (ESI) *m/z* 283 (M - 1).

Example 100(c) *1-[4-Bromo-2-(trifluoromethoxy)benzoyl]azetidine*

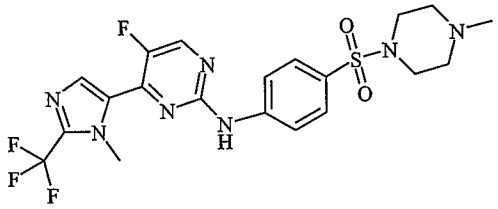


The title compound was prepared in accordance with the general method H using 4-bromo-2-(trifluoromethoxy)benzoic acid (300 mg, 1.05 mmol, obtained from Example 100(b)) and azetidine (70 mg, 1.22 mmol) to give the title compound (200 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.50 (dd, *J*=8.21, 1.64 Hz, 1 H) 7.45 - 7.48 (m, 1 H) 7.38 (d, *J*=8.08 Hz, 1 H) 4.21 (t, *J*=7.71 Hz, 2 H) 4.00 (t, *J*=7.58 Hz, 2 H) 2.34 (dd, 18 H); MS (ESI) *m/z* 324 (M + 1).

Example 101

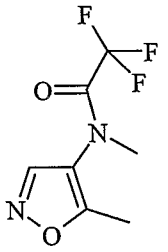
5-Fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-amine hydrochloride



The title compound was prepared in accordance with the general method E using 5-Fluoro-4-[1-methyl-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 101(e)) (35 mg, 0.135 mmol) and 1-[(4-bromophenyl)sulfonyl]-4-methylpiperazine (described in WO 2003004472) (38 mg, 0.12 mmol) to give (47 mg, 78%). The hydrochloride was prepared in accordance with that described in general method D.

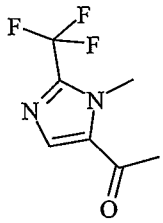
^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.6-10.3 (m, 2 H), 8.82 (s, 1 H), 7.99 (s, *J* = 8.4 Hz, 2 H), 7.9-7.7 (m, 3 H), 4.13 (s, 3 H), 3.8–3.6 (m, 2 H), 3.5–3.3 (m, 2 H), 3.3–3.0 (m, 2 H), 2.73 (s, 3 H), 2.7–2.5 (m, 2 H); MS (ES) *m/z* 500 (M+1).

Example 101(a) *2,2,2-Trifluoro-N-methyl-N-(5-methylisoxazol-4-yl)acetamide*



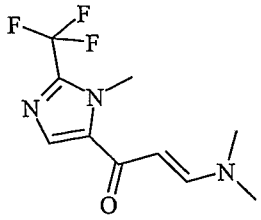
Trifluoroacetic anhydride (10 mL, 71 mmol) in CH_2Cl_2 (100 mL) was added to *N*,5-dimethylisoxazol-4-amine (Reiter, L.A., *J. Org. Chem.* **1987**, *52*, 2714-2726) (6.68g, 59.6 mmol) in DCM (200 mL) and pyridine (6 mL, 74 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and at r.t. for 2 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with H_2O and saturated $NaHCO_3$ (aq). The organic layer was dried (Na_2SO_4), concentrated *in vacuo* to give the title compound (12.4 g, 100%) as a solid.
MS (ESI) *m/z* 208 (M^+).

Example 101(b) *1-[1-Methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]ethanone*



2,2,2-trifluoro-*N*-methyl-*N*-(5-methylisoxazol-4-yl)acetamide (12.4 g , 59.6 mmol, obtained from Example 1(a)) in EtOH (30 ml) was hydrogenated over Pd/C (10%, 1.0 g) at 50 psi. The reaction mixture was stirred at +50 °C overnight. Sodium methoxide (5.0 g, 87.7 mmol) was added and the resulting mixture was heated to reflux overnight. The mixture was filtered through diatomaceous earth and the residue was diluted with saturated $NaHCO_3$ (aq.) and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (Heptane:EtOAc 2: 1) to give the title compound (6.1 g, 52%) as an oil.
^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.77 (s, 1 H), 4.07 (s, 3 H), 2.54 (s, 3 H);
MS (ESI) *m/z* 192 (M^+).

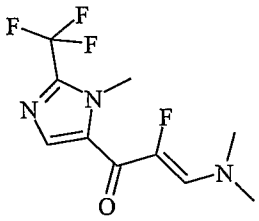
Example 101(c) *(2E)-3-(Dimethylamino)-1-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]prop-2-en-1-one*



1-[1-methyl-2-(trifluoromethyl)-1*H*-imidazol-5-yl]ethanone (6.0 g, 31 mmol, obtained from Example 101(b)) was dissolved in DMFDMA/DMF (1:1, 46 mL) and the mixture was stirred at +100 °C overnight. After cooling to r.t. the mixture was diluted with H_2O and extracted with CH_2Cl_2 (three times). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound (7.11 g, 93%) as a solid.

MS (ESI) *m/z* 247 (M^+); MS (ESI) *m/z* 248 (M + 1).

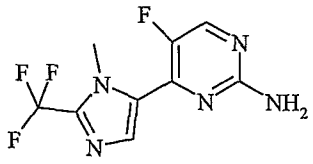
Example 101(d) *(2Z)-3-(Dimethylamino)-2-fluoro-1-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]prop-2-en-1-one*



Selectfluor (10.9 g, 30.8 mmol) was added in portions to a stirred solution of (2*E*)-3-(dimethylamino)-1-[1-methyl-2-(trifluoromethyl)-1*H*-imidazol-5-yl]prop-2-en-1-one (7.0 g, 28.3 mmol, obtained from Example 101(c)) in CH_3CN (250 mL) at 0 °C. After stirring at 0 °C for 1.5 h the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (three times). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude title compound that was used in the next step whitout any futher purification.

MS (ESI) *m/z* 265 (M^+); MS (ESI) *m/z* 266 (M + 1).

Example 101(e) *5-Fluoro-4-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine*

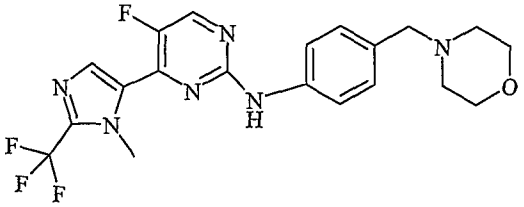


A reaction mixture of (2Z)-3-(dimethylamino)-2-fluoro-1-[1-methyl-2-(trifluoromethyl)-1*H*-imidazol-5-yl]prop-2-en-1-one (28 3 mmol, crude from Example 101(d)), guanidine carbonate (13.5 g, 75 mmol) and NaOMe (6.5 g, 120 mmol) in 1-butanol (250 mL) was heated to reflux under argon atmosphere for 2.5 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phases were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (Heptane:EtOAc 1: 1 to Heptane:EtOAc 1: 2) to give the title compound (1.76 g, 21%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.27 (d, *J*=3.03 Hz, 1 H) 7.74 (d, *J*=4.04 Hz, 1 H) 5.02 (br. s., 2 H) 4.14 (s, 3 H); MS (ESI) *m/z* 261 (M^+).

Example 102

5-Fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]-pyrimidin-2-amine hydrochloride



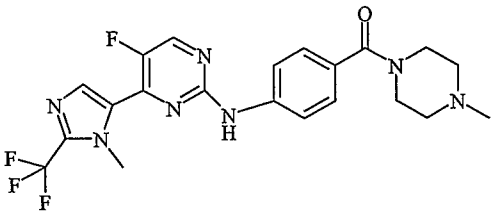
The title compound was prepared in accordance with the general method E using 5-fluoro-4-[1-methyl-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 101(e)) (35 mg, 0.135 mmol) and 4-(4-bromobenzyl)-morpholine (34 mg, 0.134 mmol) to give (48 mg, 83%). The hydrochloride was prepared in accordance to that described in general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.95 (br s, 1 H), 10.00 (s, 1 H), 8.73 (s, 1 H), 7.9-7.7 (m, 3 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 4.26 (d, *J* = 4 Hz, 2 H), 4.10 (s, 3 H), 3.93 (d, *J* = 12

Hz, 2 H), 3.77 (d, J = 12 Hz, 2 H), 3.23 (d, J = 12 Hz, 2 H), 3.1-3.0 (m, 2 H); MS (ESI) *m/z* 437 (M+1)

Example 103

[4-[5-Fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-yl]aminophenyl]-(4-methylpiperazin-1-yl)-methanone hydrochloride

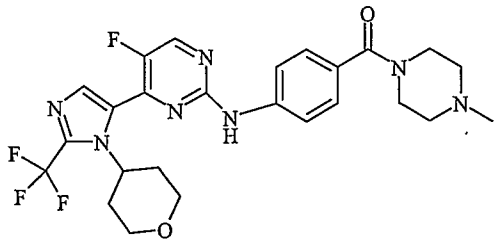


The title compound was prepared in accordance with the general method E using 5-fluoro-4-[1-methyl-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 101(e)) (35 mg, 0.135 mmol) and 1-(4-bromobenzoyl)-4-methylpiperazine (36 mg, 0.127 mmol) to give (30 mg, 51% yield). The hydrochloride was prepared in accordance to that described in general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.84 (br s, 1 H), 10.10 (s, 1 H), 8.76 (s, 1 H), 7.9-7.7 (m, 3 H), 7.45 (d, J = 8.4 Hz, 2 H), 4.2-4.0 (m, 5 H), 3.6–3.2 (m), 3.2–3.0 (m, 2 H), 2.77 (s, 3 H); hydrogens in the region 3.6–3.2 ppm were not integrated due to the overlap with the water peak; MS (ESI) *m/z* 464 (M+1)

Example 104

[4-[5-Fluoro-4-[3-tetrahydropyran-4-yl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-yl]aminophenyl]-(4-methylpiperazin-1-yl)-methanone hydrochloride



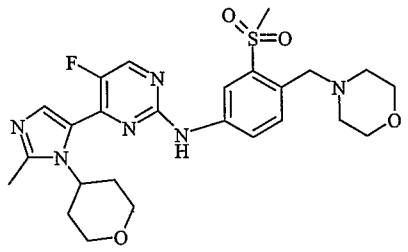
The title compound was prepared in accordance with the general method E and work-up procedure B. The product was purified by flash chromatography (CH_2Cl_2/MeOH 30:1, 20:1 then 15:1). Using 5-fluoro-4-[1-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 34(d)) (33 mg, 0.1 mmol), 1-(4-

bromobenzoyl)-4-methylpiperazine (0.027 g, 0.095 mmol), Cs_2CO_3 (65 mg, 0.2 mmol), $Pd_2(dba)_3$ (6.8 mg, 0.0075 mmol) and X-Phos (7 mg, 0.015 mmol), the base of the title compound (35 mg, 70%) was obtained as a solid. The hydrochloride was prepared in accordance with the method described in general method D.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.60 (br s, 1 H), 10.11 (s, 1 H), 8.82 (s, 1 H), 7.74 (d, J = 8.4 Hz, 2 H), 7.56 (s, 1 H), 7.42 (d, J = 8.4 Hz, 2 H), 4.80 (t, 1 H), 3.80 (d, J = 8.4 Hz, 2 H), 3.22 (t, J = 11.5 Hz, 2 H), 3.2-3.0 (m, 2 H), 2.78 (s, 3 H), 2.2–2.1 (m, 2 H), 2.0-1.8 (m, 2 H); 6 Hydrogens were not assigned in the region 3.6 -2.2 ppm due to the presence of the water and DMSO peaks in this region; MS (ESI) *m/z* 534.5 (M+1); MS (ESI) *m/z* 532.5 (M-1).

Example 105

5-Fluoro-N-[3-(methylsulfonyl)-4-(morpholin-4-ylmethyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride

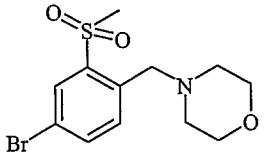


The title compound was prepared in accordance with the general method E (Workup procedure C), with the exception that the base of the product was purified by flash chromatography (gradient from 100 % CH_2Cl_2 to 6 % MeOH in CH_2Cl_2) before final purification by preparative HPLC. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (35 mg, 0.13 mmol), 4-[4-bromo-2-(methylsulfonyl)benzyl]morpholine (obtained from Example 105(a)) (46 mg, 0.14 mmol), Cs_2CO_3 (66 mg, 0.20 mmol), $Pd_2(dba)_3$ (6 mg, 0.006 mmol) and X-Phos (8 mg, 0.017 mmol), the base of the title compound (23 mg, 32%) was obtained as a solid. The hydrochloride was prepared in accordance with the method described in general method D.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.47 (br.s., 1 H) 10.40 (s, 1 H) 8.88 (d, 1 H) 8.33 (s, 1 H) 8.22 (d, 1 H) 8.07 (s, 1 H) 7.98 (br.s., 1 H) 5.00 - 4.87 (m, 1 H) 4.62 (br.s., 2 H)

4.03 - 3.72 (m, 6 H) 2.82 (s, 3 H) 2.24 - 2.09 (m, 2 H) 2.02 - 1.90 (m, 2 H) additional protons obscured by the HDO signal; MS (ESI) *m/z* 531 (M+1).

Example 105(a) *4-[4-Bromo-2-(methylsulfonyl)benzyl]morpholine*

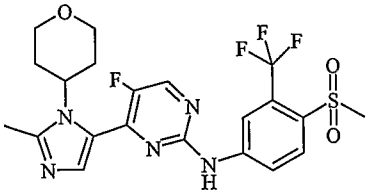


To a stirred solution of 4-bromo-2-(methylsulfonyl)benzaldehyde (0.20 g, 0.76 mmol) in MeOH (1.5 mL) was added morpholine (0.073 g, 0.84 mmol), $NaCNBH_3$ (0.072 g, 1.1 mmol) and HOAc (0.091 g, 1.5 mmol) and the reaction was stirred at r.t. over night. The solvent was removed *in vacuo* and the crude product was partitioned between EtOAc / 1M $NaHCO_3$ (aq.). The organic phase was dried (Na_2SO_4), filtered concentrated and purified by flash chromatography (gradient from 100% heptane to 40% EtOAc in heptane) to give the title compound as a solid (0.088 g, 35%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.03 (d, 1 H) 7.90 (dd, 1 H) 7.56 (d, 1 H) 3.82 (s, 2 H) 3.59 - 3.51 (m, 4 H) 3.48 (s, 3 H) 2.44 - 2.35 (m, 4 H); MS (ESI) *m/z* 336 (M+1).

Example 106

5-Fluoro-N-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride



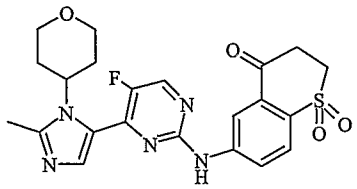
The title compound was prepared in accordance with the general method E (Workup procedure C), with the exception that the base of the product was purified by flash chromatography (gradient from 100 % EtOAc to 10 % MeOH in EtOAc). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (40 mg, 0.14 mmol), 4-bromo-1-(methylsulfonyl)-2-(trifluoromethyl)benzene (43 mg, 0.14 mmol), Cs_2CO_3 (85 mg, 0.26 mmol), $Pd_2(dba)_3$ (8 mg, 0.009 mmol) and X-Phos (9 mg, 0.018 mmol), the base of the title compound (64 mg,

83%) was obtained as a solid. The hydrochloride was prepared in accordance with the method described within general method D.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.64 (s, 1 H) 8.94 (d, 1 H) 8.30 - 8.21 (m, 2 H) 8.16 – 8.01 (m, 2 H) 4.99 - 4.87 (m, 1 H) 3.84 (dd, 2 H) 3.23 (s, 3 H) 3.28 - 3.20 (m, 2 H signal partly obscured by the HDO signal) 2.80 (s, 3 H) 2.24 - 2.09 (m, 2 H) 1.94 (dd, 2 H); MS (ESI) *m/z* 500 (M+1).

Example 107

6-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)-2,3-dihydro-4H-thiochromen-4-one 1,1-dioxide hydrochloride

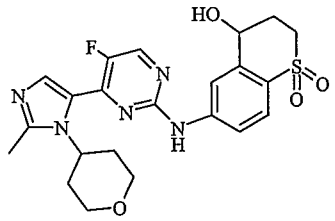


The title compound was prepared in accordance with the general method E (Workup procedure C), with the exception that the base of the product was purified by flash chromatography twice [(i) gradient from 100 % EtOAc to 10 % MeOH in EtOAc, (ii) gradient from heptane / CH_2Cl_2 7:3 to 3 % MeOH in heptane / CH_2Cl_2 7:3] followed by precipitation from a solution in MeOH / CH_2Cl_2 1:3 by addittion of toluene. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (51 mg, 0.18 mmol), 6-chloro-2,3-dihydro-4H-thiochromen-4-one 1,1-dioxide (46 mg, 0.20 mmol), Cs_2CO_3 (95 mg, 0.29 mmol), $Pd_2(dba)_3$ (9 mg, 0.010 mmol) and X-Phos (10 mg, 0.021 mmol), the base of the title compound (20 mg, 23%) was obtained as a solid. The hydrochloride was prepared in accordance with the method described in general method D with the exception that the salt was precipitated from a CH_3CN / CH_2Cl_2 solution.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.45 (s, 1 H) 8.89 (d, 1 H) 8.26 (d, 1 H) 8.21 (dd, 1 H) 8.03 (br. s., 1 H) 7.89 (d, 1 H) 5.03 - 4.90 (m, 1 H) 3.95 (t, 2 H) 3.82 (dd, 2 H) 3.26 - 3.21 (m, 2 H signal partly obscured by the HDO signal) 3.16 (t, 2 H) 2.79 (s, 3 H) 2.23 - 2.08 (m, 2 H) 1.93 (dd, 2 H); MS (ESI) m/z 470 (M-1).

Example 108

6-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)thiochroman-4-ol 1,1-dioxide hydrochloride

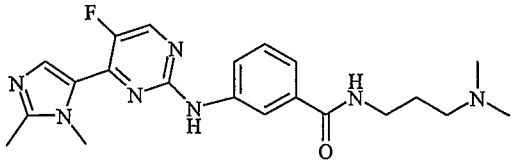


The title compound was prepared in accordance with the general method E (Workup procedure C), with the exception that the base of the product was purified by flash chromatography (gradient from 100 % CH_2Cl_2 to 5 % MeOH in CH_2Cl_2). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (52 mg, 0.18 mmol), 6-chlorothiochroman-4-ol 1,1-dioxide (Boissier, Jacques R.; Ratouis, Roger, Fr. M. (1970), FR 7499) (46 mg, 0.20 mmol), Cs_2CO_3 (95 mg, 0.29 mmol), $Pd_2(dba)_3$ (8 mg, 0.009 mmol) and X-Phos (9 mg, 0.019 mmol), the base of the title compound (10 mg, 12%) was obtained as a solid. The hydrochloride was prepared in accordance with the general method D.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.19 (s, 1 H) 8.83 (d, 1 H) 7.98 (br. s., 1 H) 7.87 (dd, 1 H) 7.79 (d, 1 H) 7.66 (d, 1 H) 5.81 (br s, 1 H) 5.05 - 4.90 (m, 1 H) 4.76 – 4.66 (m, 1 H) 3.83 (dd, 2 H) 3.60 - 3.45 (m, 2 H) 3.14 (q, 2 H) 2.76 (s, 3 H) 2.5 - 2.40 (m, 1 H) 2.36 - 2.23 (m, 1 H) 2.23 - 2.07 (m, 2 H) 1.98 - 1.85 (m, 2 H); MS (ESI) *m/z* 474 (M+1).

Example 109

N-(3-Dimethylaminopropyl)-3-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]benzamide

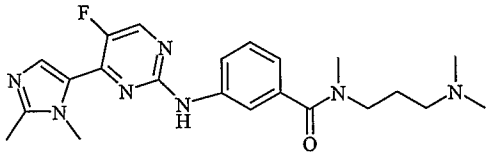


The title compound was prepared in accordance with the general method G using preparative HPLC (gradient from 0 % to 40 % acetonitrile in ammonium acetate buffer) for purification. Using methyl 3-{[4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}benzoate (44 mg, 0.129 mmol, obtained from Example 59), $Al(CH_3)_3$ (54 mg,

0.75 mmol, 2.0 M in toluene) and N,N-dimethylpropane-1,3-diamine (0.89 mg, 0.87 mmol), the title compound (45 mg, 84%) was obtained as a solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.70 (s, 1 H) 8.53 (d, 1 H) 8.42 (t, 1 H) 8.12 (s, 1 H) 7.82 - 7.75 (m, 1 H) 7.56 (d, 1 H) 7.43 - 7.32 (m, 2 H) 3.92 (s, 3 H) 2.40 (s, 3 H) 2.25 (t, 2 H) 2.13 (s, 6 H) 1.71 - 1.58 (m, 2 H); MS (ESI) *m/z* 412 (M+1).

Example 110

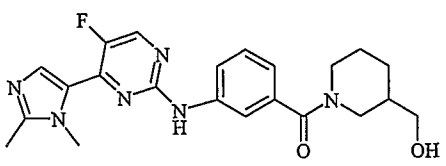
N-(3-Dimethylaminopropyl)-3-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-N-methyl-benzamide hydrochloride



The title compound was prepared in accordance with the general method G using preparative HPLC (gradient from 5 % to 45 % acetonitrile in ammonium acetate buffer) for purification. Using methyl 3-{[4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}benzoate (51 mg, 0.149 mmol, obtained from Example 59), $Al(CH_3)_3$ (107 mg, 1.49 mmol, 2.0 M in toluene) and N,N',N'-trimethylpropane-1,3-diamine (0.89 mg, 0.87 mmol), the base of the title compound (38 mg, 51%) was obtained as a solid. The hydrochloride was prepared in accordance with the method described in general method D.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.32 (br. s., 1 H) 9.99 (br. s., 1 H) 8.76 (d, 1 H) 8.17 (d, 1 H) 7.79 - 7.68 (m, 2 H) 7.39 (t, 1 H) 7.06 (br. s., 1 H) 4.02 (s, 3 H) 3.56 - 3.47 (m, 2 H) 3.13 - 3.02 (m, 2 H) 2.94 (br. s., 3 H) 2.77 (br. s., 6 H) 2.67 (s, 6 H) 2.05 - 1.93 (m, 2 H); MS (ESI) *m/z* 426 (M+1).

Example 111

[3-[[4-(2,3-Dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]-[3-(hydroxymethyl)-1-piperidyl]methanone

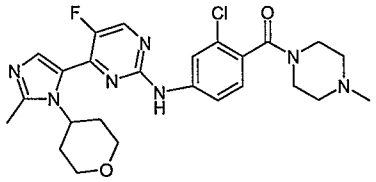


The title compound was prepared in accordance with the general method G using preparative HPLC (gradient from 10 % to 50 % acetonitrile in ammonium acetate buffer) for purification. Using methyl 3-{[4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}benzoate (53 mg, 0.155 mmol, obtained from Example 59), $Al(CH_3)_3$ (108 mg, 1.50 mmol, 2.0 M in toluene) and 3-piperidylmethanol (0.102 mg, 0.89 mmol), the title compound (56 mg, 85%) was obtained as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.96 (s, 1 H) 8.75 (d, 1 H) 8.16 (d, 1 H) 7.70 (s, 1 H) 7.71 (d, 1 H) 7.37 (t, 1 H) 6.98 (d, 1 H) 4.01 (s, 3 H) 3.72 (br. s., 1 H) 3.02 - 2.90 (m, 1 H) 2.83 - 2.69 (m, 1 H) 2.66 (s, 3 H) 1.78 - 1.68 (m, 2 H) 1.58 (br. s., 2 H) 1.41 (br. s., 1 H) 1.27 - 1.12 (m, 1 H); MS (ESI) *m/z* 425 (M+1).

Example 112

***N*-{3-Chloro-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**

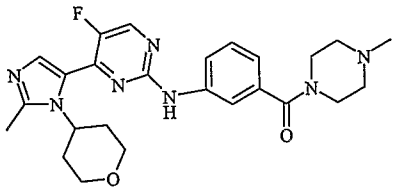


The title compound was prepared in accordance with the general method E (Workup procedure C). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (33.1 mg, 0.119 mmol), 1-(2,4-dichlorobenzoyl)-4-methylpiperazine (33.0 mg, 0.120 mmol), Cs_2CO_3 (62.0 mg, 0.190 mmol), $Pd_2(dba)_3$ (6.0 mg, 0.0065 mmol) and X-Phos (7.0 mg, 0.015 mmol), the title compound was obtained (34.1 mg, 56%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.89 (s, 1 H) 8.65 (d, 1 H) 7.85 (d, 1 H) 7.61 (dd, 1 H) 7.35 (d, 1 H) 7.25 (d, 1 H) 4.92 - 5.08 (m, 1 H) 3.57 - 3.67 (m, 2 H) 3.13 - 3.18 (m, 2 H) 3.08 - 3.13 (m, 2 H) 2.55 (s, 3 H) 2.30 - 2.41 (m, 4 H) 2.22 - 2.28 (m, 4 H) 2.19 (s, 3 H) 1.83 (d, 2 H); MS (ESI) *m/z* 514 (M+1).

Example 113

5-Fluoro-*N*-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine

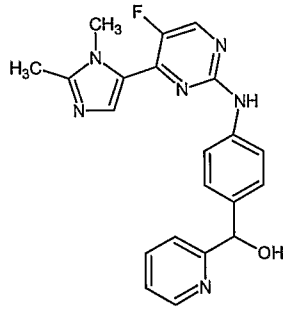


The title compound was prepared in accordance with the general method E (Workup procedure C). Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (32.3 mg, 0.116 mmol), 1-(3-chlorobenzoyl)-4-methylpiperazine (28.0 mg, 0.117 mmol), Cs_2CO_3 (60.0 mg, 0.184 mmol), $Pd_2(dba)_3$ (6.0 mg, 0.0065 mmol) and X-Phos (7.0 mg, 0.015 mmol), the title compound was obtained (31.0 mg, 56%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.67 (s, 1 H) 8.59 (d, 1 H) 7.69 (d, 1 H) 7.66 - 7.63 (m, 1 H) 7.34 - 7.30 (m, 2 H) 6.97 (d, 1 H) 3.86 - 3.78 (m, 2 H) 3.12 (t, 2 H) 2.53 (s, 3 H) 2.36 - 2.20 (m, 4 H) 2.16 (s, 3 H) 2.20 - 2.08 (m, 4 H) 1.83 - 1.74 (m, 2 H); MS (ESI) *m/z* 480 (M+1).

Example 114

(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(pyridin-2-yl)methanol



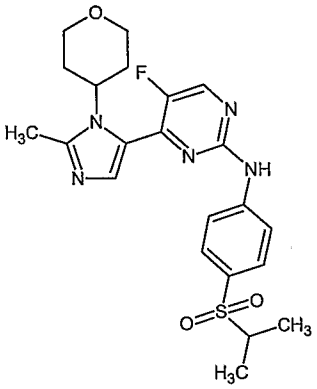
{4-[4-(2,3-Dimethyl-3H-imidazol-4-yl)-pyrimidin-2-ylamino]-phenyl}-pyridin-2-yl-methanone (obtained from Example 31) (10 mg, 0.025 mmol) was treated with $NaBH_4$ (10 mg, 0.264mmol) in EtOH (2 mL) at 0°C. The crude material was directly purified by preparative HPLC to give the title compound (2 mg, 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.59 (d, *J*=4.80 Hz, 1 H) 8.25 (d, *J*=3.28 Hz, 1 H) 7.73 (d, *J*=4.29 Hz, 1 H) 7.60 - 7.68 (m, 1 H) 7.52 (d, *J*=8.34 Hz, 2 H) 7.35 (d, *J*=8.59 Hz, 2 H)

7.20 - 7.25 (m, 1 H) 7.17 (d, *J*=7.83 Hz, 1 H) 7.05 (br. s., 1 H) 5.75 (s, 1 H) 5.30 (br. s., 1 H) 3.90 (s, 3 H) 2.48 (s, 3 H); MS (ES) *m/z* 391 (M+1).

Example 115

5-Fluoro-*N*-[4-(isopropylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine

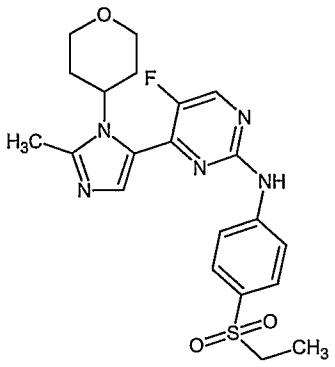


The title compound was prepared in accordance with the general method E. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (0.05 g, 0.18 mmol), 1-bromo-4-(propane-2-sulfonyl)-benzene (0.048 g, 0.18 mmol), Cs_2CO_3 (176 mg, 0.54 mmol), $Pd_2(dba)_3$ (4 mg, 0.005 mmol) and X-Phos (4 mg, 0.009 mmol), the title compound (16 mg, 20%) was obtained as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38 (d, *J*=3.03 Hz, 1 H) 7.77 - 7.82 (m, 4 H) 7.68 - 7.69 (m, 1 H) 7.66 (s, 1 H) 5.04 - 5.12 (m, 1 H) 4.11 (dd, *J*=11.62, 4.55 Hz, 2 H) 3.32 - 3.39 (m, 2 H) 3.13 - 3.23 (m, 1 H) 2.66 (s, 3 H) 2.50 - 2.62 (m, 2 H) 1.88 (m, 2 H) 1.31 (d, *J*=6.82 Hz, 6 H); MS (ES) *m/z* 458 (M-1)

Example 116

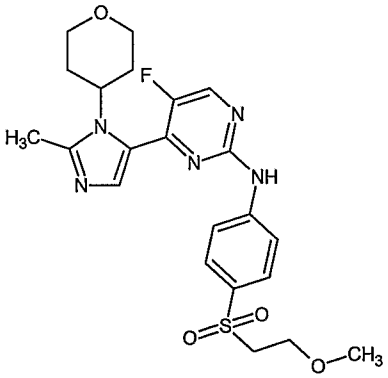
***N*-[4-(Ethylsulfonyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**



The title compound was prepared in accordance with the general method E. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (0.05 g, 0.18 mmol), 1-bromo-4-ethanesulfonyl-benzene (0.039 g, 0.18 mmol), Cs_2CO_3 (176 mg, 0.54 mmol), $Pd_2(dba)_3$ (4 mg, 0.005 mmol) and X-Phos (4 mg, 0.009 mmol), the title compound (21 mg, 26%) was obtained as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.37 (m, 1 H) 7.76 - 7.84 (m, 4 H) 7.74 (br. s., 1 H) 7.68 (d, *J*=3.79 Hz, 1 H) 5.03 - 5.13 (m, 1 H) 4.10 (dd, *J*=11.62, 4.55 Hz, 2 H) 3.29 - 3.38 (m, 2 H) 3.11 (q, *J*=7.58 Hz, 2 H) 2.66 (s, 3 H) 2.60-2.50 (m, 2 H) 1.89-1.86 (m, 1 H) 1.28 (t, *J*=7.41 Hz, 3 H); MS (ES) *m/z* 444 (M-1).

Example 117

5-Fluoro-*N*-{4-[(2-methoxyethyl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine

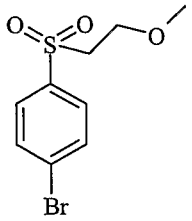


The title compound was prepared in accordance with the general method E. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (0.05 g, 0.18 mmol), 2-(4-bromophenyl)sulfonyl ethyl ether (obtained from Example 117(a)) (0.05 g, 0.18 mmol), Cs_2CO_3 (176 mg, 0.54 mmol),

$Pd_2(dba)_3$ (4 mg, 0.005 mmol) and X-Phos (4 mg, 0.009 mmol), the title compound (21 mg, 26%) was obtained as a solid.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.38 (d, *J*=2.78 Hz, 1 H) 7.75 - 7.88 (m, 4 H) 7.70 (br. s., 1 H) 7.67 (br. s., 1 H) 5.02 - 5.13 (m, 1 H) 4.11 (dd, *J*=11.62, 4.55 Hz, 2 H) 3.75 (t, *J*=6.32 Hz, 2 H) 3.29 - 3.42 (m, 4 H) 3.27 (s, 3 H) 2.66 (s, 3 H) 2.50 - 2.63 (m, 2 H) 1.88 (dd, *J*=12.24, 3.03 Hz, 2 H); MS (ES) *m/z* 474 (M-1)

Example 117(a) *2-[(4-Bromophenyl)sulfonyl]ethyl methyl ether*

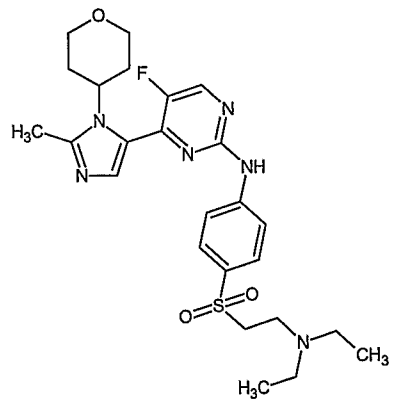


The title compound was prepared in accordance with the general method I. Using 4-bromobenzenesulfonyl chloride (0.256 g, 1 mmol), Na_2SO_3 (0.126g, 1 mmol), $NaHCO_3$ (0.252 g, 3 mmol.) and 2-bromoethyl methyl ether (0.28 mL, 3 mmol) to give the title compound (0.132 g, 50%) as an oil.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.67 - 7.83 (m, 4 H) 3.73 (t, *J*=6.06 Hz, 2 H) 3.37 (t, *J*=6.06 Hz, 2 H) 3.21 (s, 3 H); MS (ES) *m/z* 280 (M+1).

Example 118

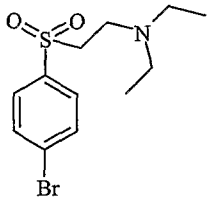
***N*-(4-{[2-(Diethylamino)ethyl]sulfonyl}phenyl)-5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine**



The title compound was prepared in accordance with the general method E. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (0.05 g, 0.18 mmol), [2-(4-bromo-benzenesulfonyl)-ethyl] -diethyl-amine (obtained from Example 118(a)) (0.058 g, 0.18 mmol), Cs_2CO_3 (176 mg, 0.54 mmol), $Pd_2(dba)_3$ (4 mg, 0.005 mmol) and X-Phos (4 mg, 0.009 mmol), the title compound (50 mg, 54%) was obtained as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.36 (d, *J*=2.78 Hz, 1 H) 7.88 (br. s., 1 H) 7.74 - 7.84 (m, 4 H) 7.62 - 7.70 (m, 1 H) 5.00 - 5.15 (m, 1 H) 4.08 (dd, *J*=11.62, 4.55 Hz, 2 H) 3.27 - 3.40 (m, 2 H) 3.19 - 3.27 (m, 2 H) 2.85 - 2.95 (m, 2 H) 2.63 (s, 3 H) 2.48 - 2.60 (m, 2 H) 2.45 (q, *J*=7.33 Hz, 4 H) 1.81 - 1.91 (m, 2 H) 0.94 (t, *J*=7.33 Hz, 6 H); MS (ES) *m/z* 515 (M-1).

Example 118(a) *2-[(4-Bromophenyl)sulfonyl]ethyl diethyl-amine*

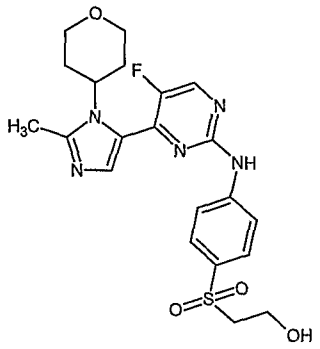


The title compound was prepared in accordance with the general method I. Using 4-bromobenzenesulfonyl chloride (0.256 g, 1 mmol), Na_2SO_3 (0.126g, 1 mmol), $NaHCO_3$ (0. 252 g, 3 mmol.) and 2-bromoethyl diethyl amine hydrobromide (0.52 g, 2 mmol) to give the title compound (0.06 g, 19%) as an oil.

^{1}H NMR (400 MHz, CDCl3) δ ppm 7.66 - 7.84 (m, 4 H) 3.19 - 3.29 (m, 2 H) 2.86 - 2.94 (m, 2 H) 2.43 (q, *J*=7.07 Hz, 4 H) 0.93 (t, *J*=7.03 Hz, 6 H); MS (ES) *m/z* 322 (M+2).

Example 119

2-{[4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)phenyl]sulfonyl}ethanol

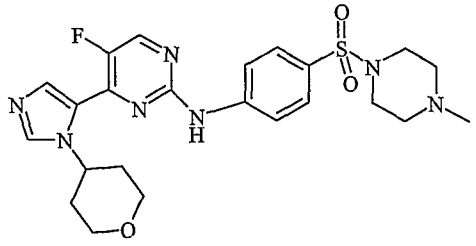


The title compound was prepared in accordance with the general method E. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (0.05 g, 0.18 mmol), 2-[(4-bromo-phenyl)sulfonyl]ethanol (described in DE3530710) (0.048 g, 0.18 mmol), Cs_2CO_3 (176 mg, 0.54 mmol), $Pd_2(dba)_3$ (4 mg, 0.005 mmol) and X-Phos (4 mg, 0.009 mmol), the title compound (40 mg, 44%) was obtained as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.37 (d, *J*=2.78 Hz, 1 H) 7.89 (s, 1 H) 7.77 - 7.86 (m, 4 H) 7.66 (d, *J*=4.04 Hz, 1 H) 5.00 - 5.12 (m, 1 H) 4.09 (dd, *J*=11.62, 4.55 Hz, 2 H) 3.96 - 4.03 (m, 2 H) 3.28 - 3.39 (m, 4 H) 2.64 (s, 3 H) 2.47 - 2.60 (m, 2 H) 1.81 - 1.92 (m, 2 H); MS (ES) *m/z* 462 (M+1)

Example 120

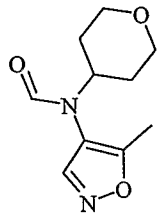
{5-Fluoro-4-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-pyrimidin-2-yl}-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-amine



The title compound was prepared in accordance with the general method E. Using 5-fluoro-4-[1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 120(e)) (0.1 g, 0.38 mmol), 1-[(4-bromophenyl)sulfonyl]-4-methylpiperazine (0.111 g, 0.349 mmol), Cs_2CO_3 (247 mg, 0.76 mmol), $Pd_2(dba)_3$ (17 mg, 0.019 mmol) and X-Phos (18 mg, 0.038 mmol), the title compound (155 mg, 88%) was obtained as an oil.

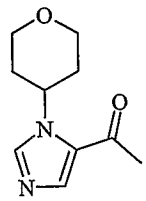
^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.38 (m, 1 H), 7.88 (m, 2 H), 7.71 (m, 4 H), 7.38 (s, 1 H), 5.35 (m, 1 H), 4.06 (m, 2H) 3.34 (m, 2 H), 3.05 (m, 4 H), 2.27 (s, 3 H), 2.12-1.98 (m, 4 H); MS (ES) *m/z* 502 (M+1).

Example 120(a) *N-(5-Methyl-isoxazol-4-yl)-N-(tetrahydro-pyran-4-yl)-formamide*



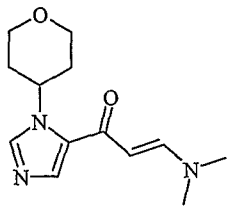
The title compound was prepared following the procedure described in Example 7(a), with the exception that the product was purified by flash chromatography (EtOAc). Using 5-methyl-4-amino-isoxazole (Reiter, L.A, *J. Org. Chem.* **1987**, *52,* 2714-2726) (2.5 g, 25.48 mmol), tetrahydro-pyran-4-one (0.26 ml, 28.03 mmol) and formic acid (3.2 g, 15.3 mmol) the title compound was obtained (3.8 g, 71 %).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (s, 1 H), 8.01 (s, 1 H), 4.67 (m, 1 H), 3.99 (m, 2 H), 3.49 (m, 1 H), 2.40 (s, 3 H), 1.72 (m, 2 H), 1.50 (m, 2 H).

Example 120(b) *5-Acetyl-1-(tetrahydro-pyran-4-yl)-1H-imidazole*



The title compound was prepared in accordance with the general method of Example 7(b), with the exception that the product was purified by flash chromatography (CH_2Cl_2/MeOH, 20:1). Using N-(5-Methyl-isoxazol-4-yl)-N-(tetrahydro-pyran-4-yl)-formamide (3.8 g, 18.1 mmol, obtained from Example 120(a)) the title compound was obtained (2.7 g, 77%).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (m, 2 H) 5.15 (m, 1 H) 4.09 (m, 2 H) 3.57 (m, 2 H) 2.48 (s, 3 H) 2.06 (m, 2 H) 1.92 (m, 2 H).

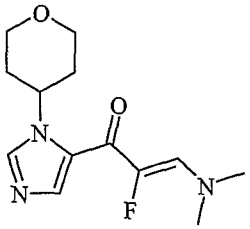
Example 120(c) *(E)-3-Dimethylamino-1-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-propenone*



The title compound was prepared in accordance with the general method of Example 7(c), with the exception that the product was purified by flash chromatography (CH_2Cl_2/MeOH, 25:1). Using 5-acetyl-1-(tetrahydro-pyran-4-yl)-1H-imidazole (2.7 g, 13.9 mmol, obtained from Example 120(b)) the title compound was obtained (3.2 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.71-7.61 (m, 3 H) 5.53 (m, 1 H) 5.37 (m, 1 H) 4.07 (m, 2 H) 3.57 (m, 2 H) 3.10 (br. s., 3 H) 2.93 (br.s., 3H) 2.11 (m, 2 H) 1.92 (m, 2 H).

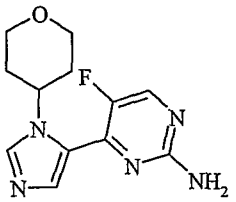
Example 120(d) (Z)-3-Dimethylamino-2-fluoro-1-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-propenone



The title compound was prepared in accordance with the general method of Example 7(d), with the exception that the product was purified by flash chromatography (EtOAc /MeOH). Using (*E*)-3-dimethylamino-1-[3-(tetrahydro-pyran-4-yl)-3*H*-imidazol-4-yl]-propenone (3.2 g, 12.85 mmol, obtained from Example 120(d)) the title compound was obtained (0.68 g, 20%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.74 (s, 1H) 7.60 (s, 1 H) 6.89 (m, 1 H) 5.10 (m, 1 H) 4.05 (m, 2 H) 3.53 (m, 2 H) 3.11 (s, 6 H) 2.08 (m, 2 H) 1.89 (m, 2 H).

Example 120(e) 5-Fluoro-4-[1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine

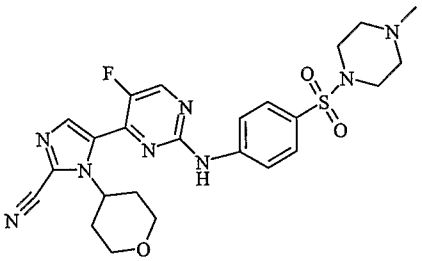


The title compound was prepared in accordance with the general method B with the exception that guanidine carbonate was used. Using (*Z*)-3-dimethylamino-2-fluoro-1-[3-(tetrahydro-pyran-4-yl)-3*H*-imidazol-4-yl]-propenone (0.67 g, 2.51 mmol, obtained from Example 120(d)) and guanidine carbonate (1.13 g, 6.27 mmol) the title compound (0.48 g, 73%) was obtained as a solid after purification by flash chromatography (CH_2Cl_2/MeOH 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.19 (m, 1 H) 7.83 (m, 2 H) 5.40 (m, 1 H) 4.89 (m, 2 H) 4.15 (m, 2H) 3.54 (m, 2 H) 2.16 (m, 2H) 2.01 (m, 2 H); MS (ES) *m/z* 264 (M+1).

Example 121

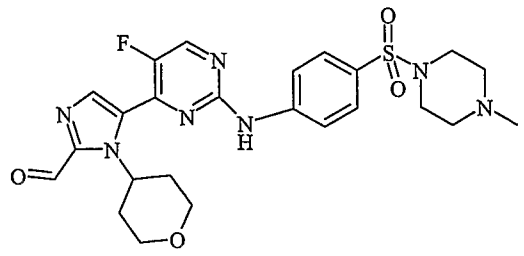
5-{5-Fluoro-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenylamino]-pyrimidin-4-yl}-1-(tetrahydro-pyran-4-yl)-1H-imidazole-2-carbonitrile



5-{5-Fluoro-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenylamino]-pyrimid in-4-yl}-1-(tetrahydro-pyran-4-yl)-1*H*-imidazole-2-carbaldehyde (obtained from Example 121(a)) (34 mg, 0.064 mmol) was mixed with $NH_2OH.HCl$ (5 mg, 0.077 mmol) in formic acid (1 mL). The mixture was heated to reflux and monitored by LC until full conversion was achieved. Then, the mixtured was extracted and purified by flash chromatography (CH_2Cl_2/MeOH) to give the title compound (21 mg, 64%).

MS (ES) *m/z* 527 (M+1).

Example 121(a) 5-{5-Fluoro-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenylamino]-pyrimidin-4-yl}-1-(tetrahydro-pyran-4-yl)-1H-imidazole-2-carbaldehyde

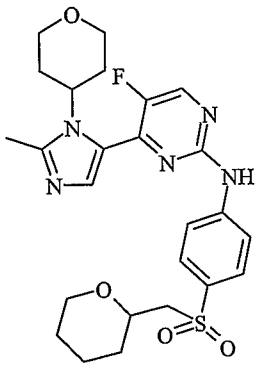


{5-Fluoro-4-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-pyrimidin-2-yl}-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-amine (obtained from Example 120) (0.315 g, 0.629 mmol) was treated with *n*-BuLi (1.8 mL, 1.6M solution in hexane, 2.83 mmol) in THF (10 mL) at low temperature (-60 to -30 °C) for 30 min. Then, DMF (0.137 mg, 1.89 mmol) was added to the mixture at -70°C and the cooling bath was removed. The resulting mixure was quenched with NH_4Cl (saturated solution) and extracted with CH_2Cl_2. The title compound (0.1 g, 30%) was obtained after purification by flash chromatography (CH_2Cl_2/MeOH 20:1).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.94 (s, 1H), 8.51 (m, 1 H), 7.79-7.68 (m, 6 H), 5.33 (m, 1 H), 4.07 (m, 2H) 3.38 (m, 2 H), 3.03 (m, 4 H), 2.71 (m, 2 H), 2.48 (m, 4 H), 2.26 (s, 3H), 1.80 (m, 4H).

Example 122

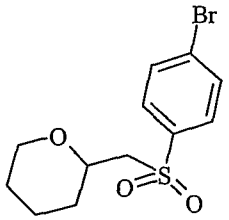
{5-Fluoro-4-[2-methyl-3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-pyrimidin-2-yl}-[4-(tetrahydro-pyran-2-ylmethanesulfonyl)-phenyl]-amine



The title compound was prepared in accordance with the general method E. Using 5-fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine (obtained from Example 7(e)) (0.05 g, 0.18 mmol), 2-(4-bromo-benzenesulfonylmethyl)-tetrahydro-pyran (obtained from Example 122(a)) (0.057 g, 0.18 mmol), Cs_2CO_3 (176 mg, 0.54 mmol), $Pd_2(dba)_3$ (4 mg, 0.005 mmol) and X-Phos (4 mg, 0.009 mmol), the title compound (21 mg, 23%) was obtained as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.37 (d, *J*=3.03 Hz, 1 H) 7.80 - 7.88 (m, 2 H) 7.71 - 7.78 (m, 2 H) 7.63 - 7.71 (m, 2 H) 4.92 - 5.19 (m, 1 H) 4.10 (dd, *J*=11.75, 4.42 Hz, 2 H) 3.76 - 3.92 (m, 2 H) 3.28 - 3.41 (m, 5 H) 3.12 (dd, *J*=14.40, 3.79 Hz, 1 H) 2.66 (s, 3 H) 2.47 - 2.61 (m, 2 H) 1.23 - 1.93 (3m, 7 H); MS (ES) *m/z* 516 (M+1).

Example 122(a) *2-(4-Bromo-benzenesulfonylmethyl)-tetrahydro-pyran*



The title compound was prepared in accordance with the general method I. Using 4-bromobenzenesulfonyl chloride (0.256 g, 1 mmol), Na_2SO_3 (0.126g, 1 mmol), $NaHCO_3$ (0.252 g, 3 mmol.) and 2-bromomethyl-tetrahydro-pyran (0.128 mL, 1 mmol) to give the title compound (0.06 g, 19%) as an oil.

MS (ES) *m/z* 321 (M+1).

Pharmaceutical compositions

According to one aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula **I,** as a free base or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, for use in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

The composition may be in a form suitable for oral administration, for example as a tablet, for parenteral injection as a sterile solution or suspension. In general the above compositions may be prepared in a conventional manner using pharmaceutically carriers or diluents. Suitable daily doses of the compounds of formula **I** in the treatment of a mammal, including man, are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician.

A compound of formula **I**, or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, can be used on its own but will usually be administered in the form of a pharmaceutical composition in which the formula **I** compound/salt/solvate (active

ingredient) is in association with a pharmaceutically acceptable excipient, diluent or carrier. Dependent on the mode of administration, the pharmaceutical composition may comprise from 0.05 to 99 %w (percent by weight), for example from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

An excipient, diluent or carrier includes water, aqueous polyethylene glycol, magnesium carbonate, magnesium stearate, talc, a sugar (such as lactose), pectin, dextrin, starch, tragacanth, microcrystalline cellulose, methyl cellulose, sodium carboxymethyl cellulose or cocoa butter.

A composition of the invention can be in tablet or injectable form. The tablet may additionally comprise a disintegrant and/or may be coated (for example with an enteric coating or coated with a coating agent such as hydroxypropyl methylcellulose).

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula **I**, or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, as hereinbefore defined, with a pharmaceutically acceptable excipient, diluent or carrier.

An example of a pharmaceutical composition of the invention is an injectable solution containing a compound of the invention, or a a pharmaceutically acceptable salt, solvate or solvate of salt thereof, as hereinbefore defined, and sterile water, and, if necessary, either sodium hydroxide or hydrochloric acid to bring the pH of the final composition to about pH 5, and optionally a surfactant to aid dissolution.

Medical use

Surprisingly, it has been found that the compounds defined in the present invention, as a free base or a pharmaceutically acceptable salt thereof, are well suited for inhibiting glycogen synthase kinase-3 (GSK3). Accordingly, the compounds of the present invention are expected to be useful in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 activity, i.e. the compounds may be used to produce an

inhibitory effect of GSK3 in mammals, including man, in need of such prevention and/or treatment.

GSK3 is highly expressed in the central and peripheral nervous system and in other tissues. Thus, it is expected that compounds of the invention are well suited for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 in the central and peripheral nervous system. In particular, the compounds of the invention are expected to be suitable for prevention and/or treatment of conditions associated with especially, dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica.

Other conditions are selected from the group consisting of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.

Further conditions are selected from the group consisting of predemented states, Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairement No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and androgenetic alopecia and Type I and Type II diabetes, diabetic neuropathy and diabetes related disorders.

One embodiment of the invention relates to the prevention and/or treatment of dementia and Alzheimer's Disease.

Another embodiment of the invention relates to the prevention and/or treatment of bone-related disorders.

The dose required for the therapeutic or preventive treatment of a particular disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated.

The present invention relates also to the use of a compound of formula **I** as defined hereinbefore, in the manufacture of a medicament for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

In the context of the present specification, the term "therapy" also includes "prevention" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention also provides for a method of treatment and/or prevention of conditions associated with glycogen synthase kinase-3 comprising administrering to a mammal, including man in need of such treatment and/or prevention a therapeutically effective amount of a compound of formula **I**, as hereinbefore defined.

Non-medical use

In addition to their use in therapeutic medicine, the compounds of formula **I** as a free base or a pharmaceutically acceptable salt thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of GSK3 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Pharmacology

Determination of ATP competition in Scintillation Proximity GSK3β Assay.

GSK3β scintillation proximity assay.

The competition experiments were carried out in duplicate with 10 different concentrations of the inhibitors in clear-bottom microtiter plates (Wallac, Finland). A biotinylated peptide substrate, Biotin-Ala-Ala-Glu-Glu-Leu-Asp-Ser-Arg-Ala-Gly-Ser(PO_3H_2)-Pro-Gln-Leu (AstraZeneca, Lund), was added at a final concentration of 1 μM in an assay buffer containing 1 mU recombinant human GSK3β (Dundee University, UK), 12 mM

morpholinepropanesulfonic acid (MOPS), pH 7.0, 0.3 mM EDTA, 0.01% β-mercaptorethanol, 0.004 % Brij 35 (a natural detergent), 0.5 % glycerol and 0.5 μg BSA/25 μl. The reaction was initiated by the addition of 0.04 μCi [γ-^{33}P]ATP (Amersham, UK) and unlabelled ATP at a final concentration of 1 μM and assay volume of 25 μl. After incubation for 20 minutes at room temperature, each reaction was terminated by the addition of 25 μl stop solution containing 5 mM EDTA, 50 μM ATP, 0.1 % Triton X-100 and 0.25 mg streptavidin coated Scintillation Proximity Assay (SPA) beads (Amersham, UK). After 6 hours the radioactivity was determined in a liquid scintillation counter (1450 MicroBeta Trilux, Wallac). The inhibition curves were analysed by non-linear regression using GraphPad Prism, USA. The K_m value of ATP for GSK3β, used to calculate the inhibition constants (K_i) of the various compounds, was 20 μM.

The following abbreviations have been used:

MOPS	Morpholinepropanesulfonic acid
EDTA	Ethylenediaminetetraacetic acid
BSA	Bovin Serum Albumin
ATP	Adenosine Triphosphate
SPA	Scintillation Proximity Assay
GSK3	Glycogen synthase kinase 3

Results

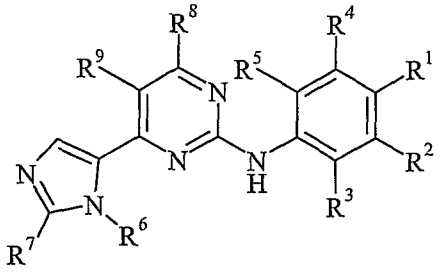
Typical K_i values for the compounds of the present invention are in the range of about 0.001 to about 10,000 nM. Other values for K_i are in the range of about 0.001 to about 1000 nM. Further values for K_i are in the range of about 0.001 nM to about 300 nM.

Table 1. Specimen results from assay.

Example no	K_i (nM)	n
1	10	3
17	14	4
22	22	3
29	126	2

CLAIMS

1. Use of a compound of the formula **I**:



I

wherein

R^1 is selected from hydrogen, halo, cyano, NO_2, C_{1-3}alkyl, C_{1-3}haloalkyl, OR^a, $SO_2NR^bR^c$, C_{0-2}alkylC(O)NR^bR^c, C_{1-4}alkylNR^bR^c, CH_2OR^h, SO_2R^i, $C(O)OR^a$, $CH(OH)R^j$ and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, CH_2OR^h, SO_2R^i, $C(O)OR^a$ and $C(O)R^j$; or

R^1 and R^2, together with the atoms to which they are attached join to form a 5- or 6-membered heterocyclic ring containing at least one N, O or S, in which any of the hydrogens of the CH_2-groups within the said heterocyclic ring can be substituted with oxo, hydroxy or halo and in which any sulphur atom within said heterocyclic ring is optionally oxidised to $-SO_2-$;

R^3 and R^5 are independently selected from hydrogen, halo, cyano, C_{1-3}alkyl, C_{1-3}haloalkyl and OR^a;

R^6 is selected from CH_3 and C_6alkyl, C_6alkenyl, C_6alkynyl and C_6haloalkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^7 is selected from hydrogen, C_{1-3}alkyl, cyano, and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more OR^a;

R^8 and R^9 are independently selected from hydrogen, cyano and halo;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl and C_{1-6}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-6}haloalkyl is optionally substituted with one or more C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a;

R^d and R^e are independently selected from hydrogen, C_{1-6}alkyl and C_{1-6}haloalkyl, wherein said C_{1-6}alkyl or C_{1-6}haloalkyl is optionally substituted with one or more OR^a; or

R^d and R^e may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

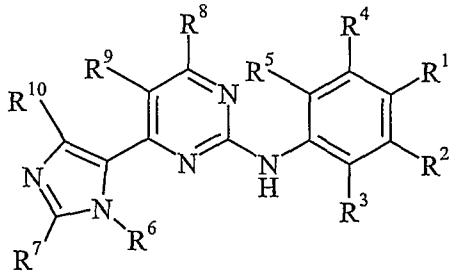
R^h is hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^i is C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-3}haloalkyl is optionally substituted with one or more halo, cyano, di-(C_{1-4}alkyl)amino-, C_{1-3}haloalkyl, C_{1-3}alkyl, heterocyclyl or OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl, OR^a, halo or cyano;
as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof;

in the manufacture of a medicament for prevention and/or treatment of dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica.

2. Use of a compound of the formula **Ia**:



Ia

wherein

R^1 is selected from hydrogen, halo, cyano, NO_2, C_{1-3}alkyl, C_{1-3}haloalkyl, OR^a, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, CH_2OR^h, SO_2R^i and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-3}alkyl, C_{1-3}haloalkyl, OR^a, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, CH_2OR^h, SO_2R^i and $C(O)R^j$;

R^3 and R^5 independently are selected from hydrogen, C_{1-3}alkyl, C_{1-3}haloalkyl and OR^a;

R^6 is selected from CH_3 and C_6alkyl, C_6alkenyl, C_6alkynyl, and C_6haloalkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^7 is selected from C_{1-3}alkyl, cyano, and C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more OR^a;

R^8 and R^9 are independently selected from hydrogen, cyano and halo;

R^{10} is hydrogen;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl or C_{1-6}haloalkyl, wherein aid C_{1-6}alkyl or C_{1-6}haloalkyl is optionally substituted with one or more OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S,

wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-3}alkyl or C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^d and R^e are independently selected from hydrogen, C_{1-6}alkyl or C_{1-6}haloalkyl, said C_{1-6}alkyl or C_{1-6}haloalkyl is optionally substituted with one or more OR^a; or

R^d and R^e may, together with the atom to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-3}alkyl or C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^h is hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy

R^i is C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl, OR^a, halo or cyano;
as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof;

in the manufacture of a medicament for prevention and/or treatment of dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica.

3. The use according to claim 1 or claim 2, wherein said compound is according to formula **I** or according to formula **Ia** and

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, SO_2R^i and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-3}haloalkyl, OR^a, $C(O)NR^bR^c$, and SO_2R^i;

R^3 and R^5 independently are selected from hydrogen, C_{1-3}alkyl, and OR^a;

R^6 is selected from CH_3, C_6alkyl and C_6haloalkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^7 is selected from C_{1-3}alkyl, cyano, and C_{1-3}haloalkyl;

R^{10} is hydrogen;

R^8 and R^9 independently are selected from hydrogen, cyano and halo;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl or C_{1-6}haloalkyl, said C_{1-6}alkyl or C_{1-6}haloalkyl is optionally substituted with one or more OR^a; or

R^b and R^c may, together with the atom to which they are attached, form a 4-, 5-, 6- or 7-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-3}alkyl or C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^i is C_{1-3}alkyl or C_{1-3}haloalkyl, said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl, OR^a, halo or cyano;
as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

4. The use according to any one of claims 1 to 3, wherein said compound is according to formula **I** or formula **Ia** and;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl;

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

5. The use according to any one of claims 1 to 4, wherein said compound is according to formula **I** or formula **Ia** and;

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, SO_2R^i and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-3}haloalkyl, OR^a, $C(O)NR^bR^c$ and SO_2R^i;

R^3 and R^5 independently are selected from hydrogen, C_{1-3}alkyl, and OR^a;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl;

R^7 is selected from C_{1-3}alkyl and C_{1-3}haloalkyl;

R^{10} is hydrogen;

R^8 and R^9 independently are selected from hydrogen and halo;

R^a is C_{1-3}alkyl or C_{1-3}haloalkyl;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, said C_{1-6}alkyl optionally substituted with one or more OR^a or

R^b and R^c may, together with the atom to which they are attached, together form a 4-, 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more halo or C_{1-3}alkyl;

R^i is C_{1-3}alkyl;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl, OR^a, halo or cyano

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

6. The use according to claim 1, wherein said compound is according to formula **I** and

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, C_{0-2}alkylC(O)NR^bR^c, C_{1-4}alkylNR^bR^c, SO_2R^i, $C(O)OR^a$, $CH(OH)R^j$ and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, SO_2R^i, $C(O)NR^bR^c$ and $C(O)OR^a$; or

R^1 and R^2, together with the atoms to which they are attached join to form a 5- or 6-membered heterocyclic ring containing at least one N, O or S, in which any of the hydrogen sof the CH_2-groups within the said heterocyclic ring can be substituted with oxo, hydroxy or halo and in which any sulphur atom within said heterocyclic ring is optionally oxidised to $-SO_2-$;

R^3 and R^5 are independently selected from hydrogen, C_{1-3}alkyl, and OR^a;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N or O, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl;

R^7 is selected from C_{1-3}alkyl, cyano, and C_{1-3}haloalkyl;

R^8 and R^9 are independently selected from hydrogen and halo;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl and heterocyclyl, wherein said C_{1-6}alkyl, heterocyclyl is optionally substituted with one or more cyano, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a;

R^d and R^e are independently selected from hydrogen and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more OR^a; or

R^d and R^e may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo;

R^i is selected from C_{1-6}alkyl and heterocyclyl, wherein said C_{1-6}alkyl or heterocyclyl is optionally substituted with one or more di-(C_{1-4}alkyl)amino-, heterocyclyl or OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl;

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

7. The use according to claim 1, wherein said compound is according to formula **I** and R^3 and R^5 are hydrogen.

8. The use according to claim 7, wherein R^8 is hydrogen and R^9 is hydrogen or fluoro.

9. The use according to claim 8, wherein R^6 is C_6alkyl.

10. The use according to claim 8, wherein R^6 is tetrahydropyran.

11. The use according to any one of claims 7 to 10, wherein R^7 is methyl or trifluoromethyl.

12. The use according to any one of claims 7 to 11, wherein R^4 is selected from hydrogen, halo, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, SO_2R^i, $C(O)NR^bR^c$ and $C(O)OR^a$.

13. The use according to any one of claims 7 to 11, wherein R^4 is $C(O)NR^bR^c$ and wherein R^b and R^c are independently selected from hydrogen and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more OR^a and wherein R^a is C_{1-3}alkyl.

14. The use according to claim 12, wherein R^4 is trifluoromethyl.

15. The use according to claim 12, wherein R^4 is chloro.

16. The use according to claim 12, wherein R^a is trifluoromethyl.

17. The use according to any one of claim 7 to 12, wherein R^2 is hydrogen, halo, C_{1-3}alkyl or OR^a.

18. The use according to claim 17, wherein R^2 is chloro.

19. The use according to claim 17, wherein R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, C_{0-2}alkylC(O)NR^bR^c, C_{1-4}alkylNR^bR^c, SO_2R^i, C(O)OR^a, CH(OH)R^j and C(O)R^j.

20. The use according to claim 19, wherein R^1 is C_{0-2}alkylC(O)NR^bR^c and

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl andC_{1-6}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-6}haloalkyl is optionally substituted with one or more C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a.

21. The use according to claim 20, wherein R^b and R^c together with the atom to which they are attached, form a heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a.

22. The use according to claim 21, wherein said heterocyclic ring is substituted with methyl.

23. The use according to claim 19, wherein R^1 is C_{1-4}alkylNR^{b}R^c and

R^b and R^c together with the atom to which they are attached, form a heterocyclic ring.

24. The use according to claim 19, R^1 is SO_2R^i and R^i is C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more OR^a.

25. The use according to claim 24, wherein R^i is methyl.

26. The use according to claim 19, wherein R^1 is $SO_2NR^bR^c$ and

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl andC_{1-6}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-6}haloalkyl is optionally substituted with one or more C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a.

27. The use according to claim 26, wherein R^b and R^c together with the atom to which they are attached form a heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-6}alkyl or C_{1-3}haloalkyl.

28. The use according to claim 27, wherein said heterocyclic ring is substituted with a C_{1-6}alkyl.

29. The use according to claim 28, wherein said C_{1-6}alkyl is methyl.

30. Use of a compound according to claim 1 or claim 2 selected from:

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[3-methoxy-5-(trifluoromethyl)phenyl]pyrimidin-2-amine;

N-(3,5-Dichlorophenyl)-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(phenyl)methanone;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]-3-nitrophenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-[(4-methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{3-methoxy-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-[(4-methylpiperazin-1-yl)carbonyl]-3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-[(4-methylpiperazin-1-yl)sulfonyl]-3-(trifluoromethoxy)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

[4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)phenyl](pyridin-2-yl)methanone hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(trifluoromethyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

3-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzonitrile hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(pyridin-2-yl)methanone hydrochloride;

4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzonitrile hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(piperazin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

N-{4-[(Dimethylamino)methyl]phenyl}-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(1-morpholin-4-ylethyl)phenyl]pyrimidin-2-amine;

N-[4-(1-Azetidin-1-ylethyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(2-morpholin-4-ylethyl)phenyl]pyrimidin-2-amine;

N-[4-(Methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{4-[(4-Methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{4-[(4-Methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

4-[2-Methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine;

4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(morpholin-4-ylsulfonyl)phenyl]pyrimidin-2-amine;

N-(4-{[4-(2-Methoxyethyl)piperazin-1-yl]sulfonyl}phenyl)-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{4-[(4-Isopropylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

4-[2-Methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]-N-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine;

(N-(1-Methylpiperidin-4-yl)-4-({4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzenesulfonamide;

N-{4-[(4-Methyl-1,4-diazepan-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N,N-Diethyl-4-({4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzenesulfonamide;

N-[4-(Azetidin-1-ylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{3-[(4-Methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{3-Chloro-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-{3-Methyl-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-N-(4-{[(3R)-3-methylmorpholin-4-yl]sulfonyl}phenyl)-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-N-{3-methyl-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-N-(4-{[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]sulfonyl}phenyl)-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)-N,N-dimethylbenzenesulfonamide;

N-[4-(Azetidin-1-ylsulfonyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

Methyl 3-{[4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}benzoate;

3-[[4-(2,3-Dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-N-(3-methoxypropyl)benzamide hydrochloride;

[4-[[4-(2,3-Dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-2-(trifluoromethoxy)phenyl]-(4-methylpiperazin-1-yl)methanone hydrochloride;

N-[4-(Azetidin-1-ylcarbonyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

N-{4-[(3,3-Difluoroazetidin-1-yl)carbonyl]phenyl}-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-N-[3-methyl-4-(morpholin-4-ylmethyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-N-[4-(morpholin-4-ylmethyl)phenyl]-4-[3-oxan-4-yl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-amine hydrochloride;

5-Fluoro-N-{4-[(4-fluoropiperidin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

Ethyl 4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzoate;

N,N-Diethyl-4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-(3-methoxypropyl)benzamide hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-(1,4-oxazepan-4-yl)methanone hydrochloride;

(4-ethylpiperazin-1-yl)-[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-methanone hydrochloride;

(2,6-dimethylmorpholin-4-yl)-[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-methanone hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-(3-fluoropyrrolidin-1-yl)-methanone hydrochloride;

(3,3-difluoropyrrolidin-1-yl)-[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-methanone hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-methyl-benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-tetrahydropyran-4-yl-benzamide hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-(3-hydroxypyrrolidin-1-yl)-methanone hydrochloride;

N-(2-cyanoethyl)-4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-methyl-benzamide hydrochloride;

N-ethyl-4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-(2-hydroxyethyl)benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-(2-hydroxyethyl)-N-methyl-benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-(2-hydroxyethyl)benzamide hydrochloride;

N-(2-dimethylaminoethyl)-4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-benzamide hydrochloride;

(4-dimethylamino-1-piperidyl)-[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-methanone hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-[4-(2-methoxyethyl)piperazin-1-yl]-methanone hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-[2-(1-piperidyl)ethyl]benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-(2-morpholinoethyl)benzamide hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-isopropyl-benzamide hydrochloride;

N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-benzamide hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-(4-isopropylpiperazin-1-yl)-methanone hydrochloride;

[4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]aminophenyl]-(4-methyl-1,4-diazepan-1-yl)-methanone hydrochloride;

4-[5-fluoro-4-(2-methyl-3-tetrahydropyran-4-yl-imidazol-4-yl)-pyrimidin-2-yl]amino-N-tetrahydrofuran-3-yl-benzamide hydrochloride;

5-Fluoro-N-[4-(methylsulfonyl)phenyl]-4-[1-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-[4-(Azetidin-1-ylcarbonyl)phenyl]-5-fluoro-4-[1-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-[4-(Azetidin-1-ylcarbonyl)-3-chlorophenyl]-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

N-[4-(Azetidin-1-ylcarbonyl)-3-methylphenyl]-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

N-[3-Chloro-4-(methylsulfonyl)phenyl]-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoro-N-[4-(methylsulfonyl)phenyl]pyrimidin-2-amine;

N-{3-Chloro-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoro-N-{3-methyl-4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine;

N-[4-(Azetidin-1-ylcarbonyl)-3-(trifluoromethoxy)phenyl]-4-(1,2-dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

5-Fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]-pyrimidin-2-amine hydrochloride;

[4-[5-Fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-yl]aminophenyl]-(4-methylpiperazin-1-yl)-methanone hydrochloride;

[4-[5-Fluoro-4-[3-tetrahydropyran-4-yl-2-(trifluoromethyl)imidazol-4-yl]-pyrimidin-2-yl]aminophenyl]-(4-methylpiperazin-1-yl)-methanone hydrochloride;

5-Fluoro-N-[3-(methylsulfonyl)-4-(morpholin-4-ylmethyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-N-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

6-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)-2,3-dihydro-4H-thiochromen-4-one 1,1-dioxide hydrochloride;

6-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)thiochroman-4-ol 1,1-dioxide hydrochloride;

N-(3-Dimethylaminopropyl)-3-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]benzamide;

N-(3-Dimethylaminopropyl)-3-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-N-methyl-benzamide hydrochloride;

[3-[[4-(2,3-Dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]-[3-(hydroxymethyl)-1-piperidyl]methanone;

N-{3-Chloro-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-N-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

(4-{[4-(1,2-Dimethyl-1H-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(pyridin-2-yl)methanol;

5-Fluoro-N-[4-(isopropylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-[4-(Ethylsulfonyl)phenyl]-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

5-Fluoro-N-{4-[(2-methoxyethyl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

N-(4-{[2-(Diethylamino)ethyl]sulfonyl}phenyl)-5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine;

2-{[4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)phenyl]sulfonyl}ethanol;

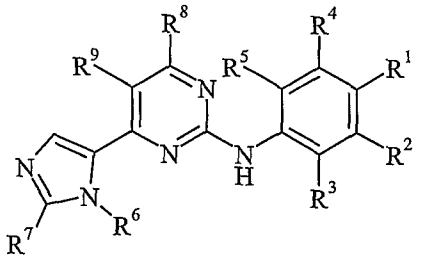
{5-Fluoro-4-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-pyrimidin-2-yl}-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-amine;

5-{5-Fluoro-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenylamino]-pyrimidin-4-yl}-1-(tetrahydro-pyran-4-yl)-1H-imidazole-2-carbonitrile; and

{5-Fluoro-4-[2-methyl-3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-pyrimidin-2-yl}-[4-(tetrahydro-pyran-2-ylmethanesulfonyl)-phenyl]-amine;

in the manufacture of a medicament for prevention and/or treatment of dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica.

31. A compound of the formula **I**:



I

wherein

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, OR^a, $SO_2NR^bR^c$, C_{0-2}alkylC(O)NR^bR^c, C_{1-4}alkylNR^bR^c, CH_2OR^h, SO_2R^i, $C(O)OR^a$, $CH(OH)R^j$ and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, $C(O)NR^bR^c$, SO_2R^i and $C(O)OR^a$; or

R^1 and R^2, together with the atoms to which they are attached form a 5- or 6-membered heterocyclic ring containing at least one N, O or S, in which any of the hydrogens of the CH_2-groups within said heterocyclic ring can be substituted with oxo, hydroxy or halo and in which any sulphur atom within said heterocyclic ring is optionally oxidised to $-SO_2-$;

R^3 and R^5 are independently selected from hydrogen, C_{1-3}alkyl and OR^a;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

R^7 is selected from hydrogen, C_{1-3}alkyl, cyano and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more OR^a;

R^8 and R^9 are independently are selected from hydrogen and halo;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl andC_{1-6}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-6}haloalkyl is optionally substituted with one or more C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a;

R^d and R^e are independently selected from hydrogen, C_{1-6}alkyl and C_{1-6}haloalkyl, wherein said C_{1-6}alkyl or C_{1-6}haloalkyl is optionally substituted with one or more OR^a; or

R^d and R^e may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy;

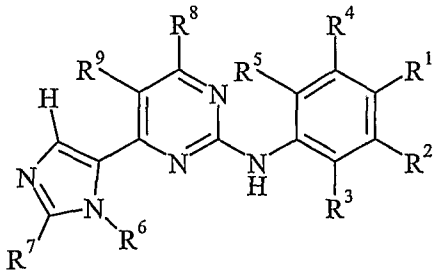
R^h is hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^i is selected from C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl and C_{1-3}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-3}haloalkyl is optionally substituted with one or more halo, cyano, di-(C_{1-4}alkyl)amino-, C_{1-3}haloalkyl, C_{1-3}alkyl, heterocyclyl or OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl, OR^a, halo or cyano;

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

32. A compound of the formula Ib:



Ib

wherein

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, $C(O)NR^bR^c$, $CH_2NR^bR^c$, CH_2OR^h, SO_2R^i and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-3}haloalkyl, OR^a, $C(O)NR^bR^c$, and SO_2R^i;

R^3 and R^5 independently are selected from hydrogen, C_{1-3}alkyl, and OR^a;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl or C_{1-3}haloalkyl;

R^7 is selected from C_{1-3}alkyl and C_{1-3}haloalkyl;

R^8 and R^9 independently are selected from hydrogen and halo;

R^a is C_{1-3}alkyl or C_{1-3}haloalkyl;

R^b and R^c are independently selected from hydrogen and C_{1-6}alkyl, optionally substituted with one or more OR^a; or

R^b and R^c may, together with the atom to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from N or O, wherein said heterocyclic ring is optionally substituted with one or more halo or C_{1-3}alkyl ;

R^h is hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, wherein said C_{1-3}alkyl or C_{1-3}haloalkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^i is C_{1-3}alkyl;

R^j is an aryl or heteroaryl ring;

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

33. A compound according to claim 31, wherein

R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, C_{0-2}alkyl$C(O)NR^bR^c$, C_{1-4}alkylNR^bR^c, SO_2R^i, $C(O)OR^a$, $CH(OH)R^j$ and $C(O)R^j$;

R^2 and R^4 are independently selected from hydrogen, halo, cyano, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, SO_2R^i, $C(O)NR^bR^c$ and $C(O)OR^a$; or

R^1 and R^2, together with the atoms to which they are attached join to form a 5- or 6-membered heterocyclic ring containing at least one N, O or S, in which any of the hydrogens of the CH_2-groups within the said heterocyclic ring can be substituted with oxo, hydroxy or halo and in which any sulphur atom within said heterocyclic ring is optionally oxidised to $-SO_2-$;

R^3 and R^5 are independently selected from hydrogen, C_{1-3}alkyl, and OR^a;

R^6 is selected from CH_3 and C_6alkyl; or

R^6 is a 6-membered heterocyclic ring containing one or more heteroatoms selected from N or O, wherein said heterocyclic ring is optionally substituted with one or more C_{1-3}alkyl;

R^7 is selected from C_{1-3}alkyl, cyano, and C_{1-3}haloalkyl;

R^8 and R^9 are independently selected from hydrogen and halo;

R^a is selected from hydrogen, C_{1-3}alkyl and C_{1-3}haloalkyl, wherein said C_{1-3}alkyl is optionally substituted with one or more C_{1-3}alkoxy;

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl and heterocyclyl, wherein said C_{1-6}alkyl, heterocyclyl is optionally substituted with one or more cyano, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a;

R^d and R^e are independently selected from C_{1-6}alkyl; or

R^d and R^e may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo;

R^i is selected from C_{1-6}alkyl and heterocyclyl, wherein said C_{1-6}alkyl or heterocyclyl is optionally substituted with one or more di-(C_{1-4}alkyl)amino-, heterocyclyl or OR^a;

R^j is an aryl or heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more C_{1-3}alkyl;

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

34. A compound according to claim 31, wherein R^3 and R^5 are hydrogen.

35. A compound according to claim 34, wherein R^8 is hydrogen and R^9 is hydrogen or fluoro.

36. A compound according to claim 35, wherein R^6 is C_6alkyl.

37. A compound according to claim 35, wherein R^6 is tetrahydropyran.

38. A compound according to any one of claims 35 to 37, wherein R^7 is methyl or trifluoromethyl.

39. A compound according to any one of claims 34 to 38, wherein R^4 is selected from hydrogen, halo, NO_2, C_{1-4}alkyl, C_{1-3}haloalkyl, OR^a, SO_2R^i, $C(O)NR^bR^c$ and $C(O)OR^a$.

40. A compound according to claim 39, wherein R^4 is $C(O)NR^bR^c$ and wherein R^b and R^c are independently selected from hydrogen and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more OR^a and wherein R^a is C_{1-3}alkyl.

41. A compound according to claim 39, wherein R^4 is trifluoromethyl.

42. A compound according to claim 39, wherein R^4 is chloro.

43. A compound according to claim 39, wherein R^a is trifluoromethyl.

44. A compound according to any one of claims 34 to 39, wherein R^2 is hydrogen, halo, C_{1-3}alkyl or OR^a.

45. A compound according to claim 44, wherein R^2 is chloro.

46. A compound according to claim 44, wherein R^1 is selected from hydrogen, cyano, C_{1-3}haloalkyl, $SO_2NR^bR^c$, C_{0-2}alkylC(O)NR^bR^c, C_{1-4}alkylNR^bR^c, SO_2R^i, $C(O)OR^a$, $CH(OH)R^j$ and $C(O)R^j$.

47. A compound according to claim 46, wherein R^1 is C_{0-2}alkylC(O)NR^bR^c and

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl andC_{1-6}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-6}haloalkyl is optionally substituted with one or more C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a.

48. A compound according to claim 47, wherein R^b and R^c together with the atom to which they are attached, form a heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a.

49. A compound according to claim 48, wherein said a heterocyclic ring is substituted with methyl.

50. A compound according to claim 46, wherein R^1 is C_{1-4}alkylNR^bR^c and

R^b and R^c together with the atom to which they are attached, form a heterocyclic ring.

51. A compound according to claim 46, wherein R^1 is SO_2R^i and R^i is C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more OR^a.

52. A compound according to claim 51, wherein R^i is methyl.

53. A compound according to claim 46, wherein R^1 is $SO_2NR^bR^c$ and

R^b and R^c are independently selected from hydrogen, C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl andC_{1-6}haloalkyl, wherein said C_{1-6}alkyl, heterocyclyl, aryl, heteroaryl or C_{1-6}haloalkyl is optionally substituted with one or more C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, methanesulphonyl-, OR^a or NR^dR^e; or

R^b and R^c may, together with the atom to which they are attached, form a heterocyclic ring wherein said heterocyclic ring is optionally substituted with one or more halo, hydroxy, cyano, di-(C_{1-4}alkyl)amino-, C_{1-6}alkyl or C_{1-3}haloalkyl, wherein said C_{1-6}alkyl or C_{1-3}haloalkyl is optionally further substituted with one or more C_{1-3}alkoxy or OR^a.

54. A compound according to claim 53, wherein R^b and R^c together with the atom to which they are attached form a heterocyclic ring, wherein said heterocyclic ring is optionally substituted with one or more halo, C_{1-6}alkyl or C_{1-3}haloalkyl.

55. A compound according to claim 54, wherein said heterocyclic ring is substituted with a C_{1-6}alkyl.

56. A compound according to claim 55, wherein said C_{1-6}alkyl is methyl.

57. A compound according to claim 31 or claim 32, said compound is selected from:
4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[3-methoxy-5-(trifluoromethyl)phenyl]pyrimidin-2-amine;
N-(3,5-Dichlorophenyl)-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(phenyl)methanone;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]-3-nitrophenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-[(4-methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-{3-methoxy-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-[(4-methylpiperazin-1-yl)carbonyl]-3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-[(4-methylpiperazin-1-yl)sulfonyl]-3-(trifluoromethoxy)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

[4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)phenyl](pyridin-2-yl)methanone hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(trifluoromethyl)phenyl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[3-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

5-Fluoro-*N*-[4-(methylsulfonyl)phenyl]-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride;

3-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzonitrile hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}pyrimidin-2-amine hydrochloride;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoro-*N*-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-2-amine hydrochloride;

(4-{[4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-yl]amino}phenyl)(pyridin-2-yl)methanone hydrochloride;

4-({5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-yl}amino)benzonitrile hydrochloride;

5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]-*N*-[4-(piperazin-1-ylsulfonyl)phenyl]pyrimidin-2-amine hydrochloride; and

5-Fluoro-*N*-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine hydrochloride.

58. A compound as defined in claims 31 to 57 for use in therapy.

59. The use according to any one of claims 1 to 30, wherein the disease is Alzheimer's Disease.

60. A compound selected from:
2-Chloro-4-(1,2-dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine;
2-Methyl-4-[(4-methylpiperazin-1-yl)carbonyl]aniline;
4-[(4-Methylpiperazin-1-yl)carbonyl]-3-nitroaniline;
4-[(4-Methylpiperazin-1-yl)carbonyl]-2-(trifluoromethoxy)aniline;
4-[*N*-Acetyl-*N*-(tetrahydro-2*H*-pyran-4-yl)]amino-5-methylisoxazole;
5-Acetyl-2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazole;
(2*E*)-3-Dimethylamino-1-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;
(2*Z*)-3-Dimethylamino-2-fluoro-1-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;
5-Fluoro-4-[2-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;
1-(4-Chloro-2-methoxybenzoyl)-4-methylpiperazine;
1-[4-Bromo-2-(methylsulfonyl)benzoyl]-4-methylpiperazine;
4-(*N*-Acetyl-*N*-cyclohexyl)amino-5-methylisoxazole;
5-Acetyl-1-cyclohexyl-2-methyl-1*H*-imidazole;
(2*E*)-3-Dimethylamino-1-(1-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one;
(2*Z*)-3-Dimethylamino-2-fluoro-1-(1-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one;
4-(1-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine;
5-Acetyl-2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazole;
(2*E*)-3-Dimethylamino-1-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;
(2*Z*)-3-Dimethylamino-2-fluoro-1-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]prop-2-en-1-one;
5-Fluoro-4-[2-methyl-1-(1-methylpiperidin-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-5-fluoropyrimidin-2-amine;

1-(tert-Butoxycarbonyl)-4-(4-bromo-benzenesulfonyl)-piperazine;

5-Acetyl-1-(tetrahydro-2*H*-pyran-4-yl)- 2-trifluoromethyl-1*H*-imidazole;

(2*E*)-3-Dimethylamino-1-[1-(tetrahydro-2*H*-pyran-4-yl)-2-trifluoromethyl-1*H*-imidazol-5-yl]prop-2-en-1-one;

(2*Z*)-3-Dimethylamino-2-fluoro-1-[1-(tetrahydro-2*H*-pyran-4-yl)-2-trifluoromethyl-1*H*-imidazol-5-yl]prop-2-en-1-one;

5-Fluoro-4-[1-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;

4-[2-Methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl]pyrimidin-2-amine;

1-[(4-Bromo-2-chlorophenyl)sulfonyl]-4-methylpiperazine;

(3*R*)-4-[(4-Bromophenyl)sulfonyl]-3-methylmorpholine;

(1*S*,4*S*)-2-[(4-Bromophenyl)sulfonyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane;

Methyl 4-bromo-2-(trifluoromethoxy)benzoate;

4-Bromo-2-(trifluoromethoxy)benzoic acid;

4-(4-Chloro-2-methylbenzyl)morpholine;

Lithium 4-({5-fluoro-4-[2-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-yl}amino)benzoate;

1-(4-Bromo-2-methylbenzoyl)azetidine;

4-Bromo-2-(trifluoromethoxy)benzoic acid;

1-[4-Bromo-2-(trifluoromethoxy)benzoyl]azetidine;

2,2,2-Trifluoro-N-methyl-N-(5-methylisoxazol-4-yl)acetamide;

1-[1-Methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]ethanone;

(2E)-3-(Dimethylamino)-1-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]prop-2-en-1-one;

(2Z)-3-(Dimethylamino)-2-fluoro-1-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]prop-2-en-1-one;

5-Fluoro-4-[1-methyl-2-(trifluoromethyl)-1H-imidazol-5-yl]pyrimidin-2-amine;

4-[4-Bromo-2-(methylsulfonyl)benzyl]morpholine;

2-[(4-Bromophenyl)sulfonyl]ethyl methyl ether;

2-[(4-Bromophenyl)sulfonyl]ethyl diethyl-amine;

N-(5-Methyl-isoxazol-4-yl)-N-(tetrahydro-pyran-4-yl)-formamide;

5-Acetyl-1-(tetrahydro-pyran-4-yl)-1H-imidazole;
(E)-3-Dimethylamino-1-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-propenone;
(Z)-3-Dimethylamino-2-fluoro-1-[3-(tetrahydro-pyran-4-yl)-3H-imidazol-4-yl]-propenone;
5-Fluoro-4-[1-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-5-yl]pyrimidin-2-amine; and
5-{5-Fluoro-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenylamino]-pyrimid in-4-yl}-1-(tetrahydro-pyran-4-yl)-1H-imidazole-2-carbaldehyde.

61. Use of the compounds according to claim 60 in the preparation of a compound of formula **I** or formula **Ib** as defined in claim 31 or claim 32.

62. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of a compound according to any one of claims 31 to 57, in association with pharmaceutically acceptable excipients, carriers or diluents.

63. Use of a compound according to claims any one of claims 31 to 57, in the manufacture of a medicament for prevention and/or treatment of predemented states, Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairement No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and androgenetic alopecia and Type I and Type II diabetes, diabetic neuropathy and diabetes related disorders.

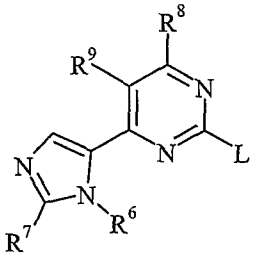
64. A method of prevention and/or treatment of dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica, comprising administrering to a mammal, including man in need of such prevention and/or treatment, a therapeutically effective amount of a compound of formula **I** as defined in any one of claims any one of claims 31 to 57.

65. The method according to claim 64, wherein the disease is Alzheimer's Disease.

66. A method of prevention and/or treatment of predemented states, Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairement No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and androgenetic alopecia and Type I and Type II diabetes, diabetic neuropathy and diabetes related disorders, comprising administrering to a mammal, including man in need of such prevention and/or treatment, a therapeutically effective amount of a compound of formula **I** as defined in any one of claims 31 to 57.

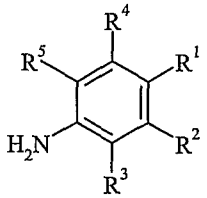
67. A process for preparing a compound of formula **I**, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, which process (wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are, unless otherwise specified, as defined in formula **I**) comprises of:

a) reaction of a pyrimidine of formula **(II)**:



(II)

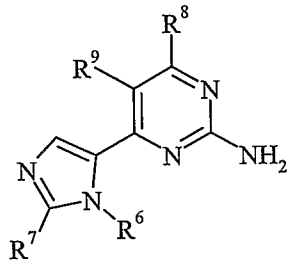
wherein L is a displaceable group; with an aniline of formula **(III)**:



(III)

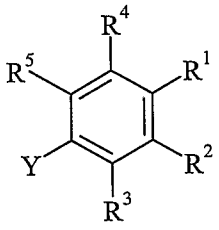
or

b) reacting a pyrimidine of formula **(IV)**:



(IV)

with a compound of formula **(V)**:



(V)

where Y is a displaceable group;

and thereafter if necessary:

i) converting a compound of the formula **I** into another compound of the formula **I**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.