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(54) Title: NOVEL COMPOUNDS FOR TREATMENT OF NEURODEGENERATION ASSOCIATED WITH DISEASES, SUCH AS ALZHEIMER'S DISEASE OR DEMENTIA

(57) Abstract: The present invention relates to novel compounds of formula (I) and their pharmaceutical compositions. In addition, the present invention relates to therapeutic methods for the treatment and/or prevention of Aβ-related pathologies such as Downs syndrome, β- amyloid angiopathy such as but not limited to cerebral amyloid angiopathy or hereditary cerebral hemorrhage, disorders associated with cognitive impairment such as but not limited to MCI ("mild cognitive impairment"), Alzheimer Disease, memory loss, attention deficit symptoms associated with Alzheimer disease, neurodegeneration associated with diseases such as Alzheimer disease or dementia including dementia of mixed vascular and degenerative origin, pre-senile dementia, senile dementia and dementia associated with Parkinson's disease, progressive supranuclear palsy or cortical basal degeneration.

Novel compounds for treatment of neurodegeneration associated with diseases, such as Alzheimer´s disease or dementia

The present invention relates to novel compounds and therapeutically acceptable salts thereof, their pharmaceutical compositions, processes for making them and their use as medicaments for treatment and/or prevention of various diseases. In particular the invention relates to compounds, which are inhibitors of β-secretase and hence inhibit the formation of amyloid β (Aβ) peptides and will be used for treatment and/or prevention of Aβ-related pathologies such as Alzheimer's disease, Downs syndrome and β-amyloid angiopathy, such as but not limited to cerebral amyloid angiopathy, hereditary cerebral hemorrhage, disorders associated with cognitive impairment, such as but not limited to MCI ("mild cognitive impairment"), Alzheimer's disease, memory loss, attention deficit symptoms associated with Alzheimer's disease, neurodegeneration associated with diseases such as Alzheimer's disease or dementia including dementia of mixed vascular and degenerative origin, pre-senile dementia, senile dementia and dementia associated with Parkinson's disease, progressive supranuclear palsy or cortical basal degeneration.

Background of the invention

The prime neuropathological event distinguishing Alzheimer's disease (AD) is deposition of the 40-42 residue amyloid β-peptide (Aβ) in brain parenchyma and cerebral vessels. A large body of genetic, biochemical and *in vivo* data support a pivotal role for Aβ in the pathological cascade that eventually leads to AD. Patients usually present early symptoms (commonly memory loss) in their sixth or seventh decades of life. The disease progresses with increasing dementia and elevated deposition of Aβ. In parallel, a hyperphosphorylated form of the microtubule-associated protein tau accumulates within neurons, leading to a plethora of deleterious effects on neuronal function. The prevailing working hypothesis regarding the temporal relationship between Aβ and tau pathologies states that Aβ deposition precedes tau aggregation in humans and animal models of the disease. Within this context, it is worth noting that the exact molecular nature of Aβ, mediating this pathological function is presently an issue under intense study. Most likely, there is a continuum of toxic species ranging from lower order Aβ oligomers to supramolecular assemblies such as Aβ fibrils.

The Aβ peptide is an integral fragment of the Type I protein APP (Aβ amyloid precursor protein), a protein ubiquitously expressed in human tissues. Since soluble Aβ can be found in both plasma and cerebrospinal fluid (CSF), and in the medium from cultured cells, APP has to undergo proteolysis. There are three main cleavages of APP that are relevant to the pathobiology of AD, the so-called α-, β-, and γ-cleavages. The α-cleavage, which occurs roughly in the middle of the Aβ domain in APP is executed by the metalloproteases ADAM10 or ADAM17 (the latter also known as TACE). The β-cleavage, occuring at the N terminus of Aβ, is generated by the transmembrane aspartyl protease Beta site APP Cleaving Enzyme1 (BACE1). The γ-cleavage, generating the Aβ C termini and subsequent release of the peptide, is effected by a multi-subunit aspartyl protease named γ-secretase. ADAM10/17 cleavage followed by γ-secretase cleavage results in the release of the soluble p3 peptide, an N-terminally truncated Aβ fragment that fails to form amyloid deposits in humans. This proteolytic route is commonly referred to as the non-amyloidogenic pathway. Consecutive cleavages by BACE1 and γ-secretase generates the intact Aβ peptide, hence this processing scheme has been termed the amyloidogenic pathway. With this knowledge at hand, it is possible to envision two possible avenues of lowering Aβ production: stimulating non-amyloidogenic processing, or inhibit or modulate amyloidogenic processing. This application focuses on the latter strategy, inhibition or modulation of amyloidogenic processing.

Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of patients with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), and other neurodegenerative disorders. Neurofibrillary tangles also occur in other neurodegenerative disorders including dementia-inducing disorders (Varghese, J., et al, Journal of Medicinal Chemistry, 2003, 46, 4625-4630). ß-amyloid deposits are predominately an aggregate of Aß peptide, which in turn is a product of the proteolysis of amyloid precursor protein (APP). More specifically, Aß peptide results from the cleavage of APP at the C-terminus by one or more γ-secretases, and at the N-terminus by ß-secretase enzyme (BACE), also known as aspartyl protease or Asp2 or Beta site APP Cleaving Enzyme (BACE), as part of the ß-amyloidogenic pathway.

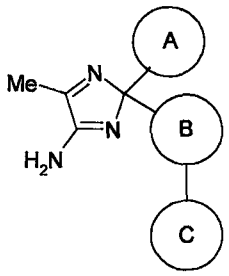
BACE activity is correlated directly to the generation of Aß peptide from APP (Sinha, et al, Nature, 1999, 402, 537-540), and studies increasingly indicate that the inhibition of BACE inhibits the production of Aßpeptide (Roberds, S. L., et al, Human Molecular Genetics, 2001, 10, 1317-1324). BACE is a membrane bound type 1 protein that is synthesized as a partially active proenzyme, and is abundantly expressed in brain tissue. It is thought to represent the major β-secretase activity, and is considered to be the rate-limiting step in the production of amyloid-β-peptide (Aβ).

Drugs that reduce or block BACE activity should therefore reduce Aβ levels and levels of fragments of Aβ in the brain, or elsewhere where Aβ or fragments thereof deposit, and thus slow the formation of amyloid plaques and the progression of AD or other maladies involving deposition of Aβ or fragments thereof. BACE is therefore an important candidate for the development of drugs as a treatment and/or prophylaxis of Aβ-related pathologies such as Downs syndrome, β-amyloid angiopathy such as but not limited to cerebral amyloid angiopathy or hereditary cerebral hemorrhage, disorders associated with cognitive impairment such as but not limited to MCI ("mild cognitive impairment"), Alzheimer Disease, memory loss, attention deficit symptoms associated with Alzheimer disease, neurodegeneration associated with diseases such as Alzheimer disease or dementia including dementia of mixed vascular and degenerative origin, pre-senile dementia, senile dementia and dementia associated with Parkinson's disease, progressive supranuclear palsy or cortical basal degeneration.
It would therefore be useful to inhibit the deposition of Aβ and portions thereof by inhibiting BACE through inhibitors such as the compounds provided herein.

The therapeutic potential of inhibiting the deposition of Aβ has motivated many groups to isolate and characterize secretase enzymes and to identify their potential inhibitors.

Outline of the invention

Provided herein are novel compounds that are active BACE inhibitors. Thus, in one aspect of the invention, there is provided compounds according to formula (I):



(I)

wherein

A is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{0-6}alkylC_{3-8}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl or C_{0-6}alkyl-C_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;

B is aryl or heteroaryl; wherein said aryl or heteroaryl is optionally substituted with one or more R^2;

C is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, $NR^4(CO)N(R^4)_2$, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)N(R^4)_2$, C_{0-6}alkylSR^4, C_{0-6}alkylOSO_2R^4, C_{0-6}alkylSO_3R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, C_{0-6}alkyl$(SO_2)N(R^4)_2$, C_{0-6}alkyl$(SO)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO_2)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO)R^4$, SF_5, and OSF_5, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, C_{0-6}alkylOR^4, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, $NR^4(CO)N(R^4)_2$, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)N(R^4)_2$, C_{0-6}alkylSR^4, C_{0-6}alkylOSO_2R^4, C_{0-6}alkylSO_3R^4, C_{0-6}alkylSO_2R^4,

C_{0-6}alkylSOR^4, C_{0-6}alkyl(SO_2)N(R^4)$_2$, C_{0-6}alkyl(SO)N(R^4)$_2$, C_{0-6}alkylNR^4(SO_2)N(R^4)$_2$, C_{0-6}alkylNR^4(SO)R^4, SF_5, and OSF_5, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl or is optionally substituted with one or more R^3; or two R^1 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^2 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkylN(R^4)$_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkylCON(R^4)$_2$, O(CO)OR^4, O(CO)R^4, O(CO)N(R^4)$_2$, NR^4(CO)OR^4, C_{0-6}alkylNR^4(CO)R^4, NR^4(CO)N(R^4)$_2$, NR^4(CO)(CO)R^4, NR^4(CO)(CO)-N(R^4)$_2$, C_{0-6}alkylSR^4, C_{0-6}alkylOSO_2R^4, C_{0-6}alkylSO_3R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, C_{0-6}alkyl(SO_2)N(R^4)$_2$, C_{0-6}alkyl(SO)N(R^4)$_2$, C_{0-6}alkylNR^4(SO_2)N(R^4)$_2$, C_{0-6}alkylNR^4(SO)-R^4 and C_{0-6}alkylOR^4, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3,
or two R^2 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^3 is selected from halogen, NO_2, CHO, C_{0-6}alkylCN, C_{0-6}alkylOR^4, C_{1-6}haloalkyl, C_{0-6}alkylN(R^4)$_2$, NR^4C(O)R^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkylCON(R^4)$_2$, C_{0-6}alkylNR^4(CO)R^4, O(CO)N(R^4)$_2$, NR^4(CO)OR^4, NR^4(CO)N(R^4)$_2$, O(CO)OR^4, O(CO)R^4, C_{0-6}alkylCOR^4, NR^4(CO)(CO)R^4, NR^4(CO)(CO)N(R^4)$_2$, C_{0-6}alkylSR^4, C_{0-6}alkyl(SO_2)N(R^4)$_2$, OC_{2-6}alkylN-R^4(SO_2)R^4, C_{0-6}alkyl(SO)N(R^4)$_2$, OSO_2R^4, SO_3R^4, C_{0-6}alkylNR^4(SO_2)N(R^4)$_2$, C_{0-6}alkylN-R^4(SO)R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkyl-C_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, and C_{0-6}alkylheterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylhetero-cyclyl is optionally substituted with one or more R^6;

R^4 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{1-6}alkylOR^5, and C_{1-6}alkyl$N(R^5)_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^4 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^5 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheterocyclyl and C_{0-6}alkylheteroaryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkyl-C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^5 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^6 is selected from oxo, halogen, nitro, CN, OR^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylheterocyclyl, C_{1-6}haloalkyl, OC_{2-6}alkyl$N(R^7)_2$, $N(R^7)_2$, $CON(R^7)_2$, $NR^7(CO)R^7$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^7, $SON(R^7)_2$, $(SO_2)N(R^7)_2$, $NR^7SO_2R^7$, NR^7SOR^7, SO_2R^7, SOR^7, $(CO)C_{1-6}$alkyl-$N(R^7)_2$, $(SO_2)C_{1-6}$alkyl$N(R^7)_2$, OSO_2R^7 and SO_3R^7, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, or C_{0-6}alkylC_{3-6}cycloalkyl is optionally substituted with one or more substituents independently selected from halo, nitro, cyano, OR^7, C_{1-6}alkyl, or C_{1-6}haloalkyl;

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_6cycloalkynyl, aryl, heteroaryl and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, cyano, halogen and OC_{1-3}alkyl; or two R^7 may together form a 4 to 6 membered

heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring being optionally substituted with one or more substituents independently selected from hydroxy, OC_{1-3}alkyl, cyano and halogen;

as a free base or a pharmaceutically acceptable salt thereof.

In one embodiment of the present invention, the molecular weight of the compound of formula (I) is more than 300 g/mol. In one embodiment of the present invention, the molecular weight of the compound of formula (I) is less than 600 g/mol.

In another embodiment of the present invention A is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{0-6}alkylC_{3-8}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl or C_{0-6}alkyl-C_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;

B is aryl or heteroaryl; wherein said aryl or heteroaryl is optionally substituted with one or more R^2;

C is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkyl-CN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, C_{0-6}alkyl$(SO)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO_2)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO)R^4$, SF_5, and OSF_5, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, C_{0-6}alkylOR^4, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, $NR^4(CO)N(R^4)_2$, $NR^4(CO)(CO)R^4$,

$NR^4(CO)(CO)N(R^4)_2$, $C_{0-6}alkylSR^4$, $C_{0-6}alkylOSO_2R^4$, $C_{0-6}alkylSO_3R^4$, $C_{0-6}alkylSO_2R^4$, $C_{0-6}alkylSOR^4$, SF_5, and OSF_5, wherein said $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, $C_{0-6}alkylheterocyclyl$ or is optionally substituted with one or more R^3, or two R^1 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^2 is selected from $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkyl-C_{3-6}cycloalkenyl$, $C_{0-6}alkylC_6cycloalkynyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, $C_{0-6}alkyl-heterocyclyl$, $C_{0-6}alkylCO_2R^4$, $C_{0-6}alkylN(R^4)_2$, halogen, $C_{0-6}alkylCN$, $C_{0-6}alkylCOR^4$, CHO, NO_2, $C_{0-6}alkylCON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, $C_{0-6}alkylNR^4(CO)R^4$, $NR^4(CO)N(R^4)_2$, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)N(R^4)_2$, $C_{0-6}alkyl-(SO)N(R^4)_2$, $C_{0-6}alkylNR^4(SO_2)N(R^4)_2$, $C_{0-6}alkylNR^4(SO)R^4$ and $C_{0-6}alkylOR^4$, wherein said $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkyl-heteroaryl$ or $C_{0-6}alkylheterocyclyl$ is optionally substituted with one or more R^3, or two R^2 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^3 is selected from halogen, NO_2, CHO, $C_{0-6}alkylCN$, $C_{0-6}alkylOR^4$, $C_{1-6}haloalkyl$, $C_{0-6}alkylN(R^4)_2$, $NR^4C(O)R^4$, $C_{0-6}alkylCO_2R^4$, $C_{0-6}alkylCON(R^4)_2$, $C_{0-6}alkylNR^4(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, $NR^4(CO)N(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $C_{0-6}alkylCOR^4$, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)N(R^4)_2$, $C_{0-6}alkylSR^4$, $C_{0-6}alkyl(SO_2)N(R^4)_2$, $OC_{2-6}alkylN-R^4(SO_2)R^4$, $C_{0-6}alkyl(SO)N(R^4)_2$, OSO_2R^4, SO_3R^4, $C_{0-6}alkylNR^4(SO_2)N(R^4)_2$, $C_{0-6}alkylN-R^4(SO)R^4$, $C_{0-6}alkylSO_2R^4$, $C_{0-6}alkylSOR^4$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkyl-C_{3-6}cycloalkyl$, $C_{0-6}alkylC_{3-6}cycloalkenyl$, $C_{0-6}alkylC_6cycloalkynyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, and $C_{0-6}alkylheterocyclyl$, wherein said $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, or $C_{0-6}alkyl-heterocyclyl$ is optionally substituted with one or more R^6;

R^4 is selected from hydrogen, $C_{1-6}alkyl$, $C_{1-3}haloalkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylC_{3-6}cycloalkenyl$, $C_{0-6}alkylC_6cycloalkynyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, $C_{0-6}alkylheterocyclyl$, $C_{1-6}alkylOR^5$, and $C_{1-6}alkylN(R^5)_2$, wherein

said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^4 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^5 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheterocyclyl and C_{0-6}alkylheteroaryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^5 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^6 is selected from oxo, halogen, nitro, CN, OR^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylheterocyclyl, C_{1-6}haloalkyl, OC_{2-6}alkyl$N(R^7)_2$, $N(R^7)_2$, $CON(R^7)_2$, $NR^7(CO)R^7$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^7, $SON(R^7)_2$, $(SO_2)N(R^7)_2$, $NR^7SO_2R^7$, NR^7SOR^7, SO_2R^7, SOR^7, $(CO)C_{1-6}$alkyl-$N(R^7)_2$, $(SO_2)C_{1-6}$alkyl$N(R^7)_2$, OSO_2R^7 and SO_3R^7, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, or C_{0-6}alkylC_{3-6}cycloalkyl is optionally substituted with one or more substituents selected from halo, nitro, cyano, OR^7, C_{1-6}alkyl, or C_{1-6}haloalkyl;

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_6cycloalkynyl, aryl, heteroaryl and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one to three substituents selected from hydroxy, cyano, halogen and OC_{1-3}alkyl; or two R^7 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring being optionally substituted with one or more substituents selected from hydroxy, OC_{1-3}alkyl, cyano and halogen.

In another embodiment of the present invention A is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{0-6}alkylC_{3-8}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl or C_{0-6}alkylC_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;

B is aryl or heteroaryl; wherein said aryl or heteroaryl is optionally substituted with one or more R^2;

C is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkyl-CN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, C_{0-6}alkyl$(SO)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO_2)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO)R^4$, SF_5, and OSF_5, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkyl-C_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkyl-heterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, C_{0-6}alkylOR^4, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, $NR^4(CO)N(R^4)_2$, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)$-$N(R^4)_2$, C_{0-6}alkylSR^4, C_{0-6}alkylOSO_2R^4, C_{0-6}alkylSO_3R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, SF_5, and OSF_5, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl or is optionally substituted with one or more R^3;

R^2 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkyl-C_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkyl-heterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$,

C_{0-6}alkyl$NR^4(CO)R^4$, $NR^4(CO)N(R^4)_2$, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)N(R^4)_2$, C_{0-6}alkyl-$(SO)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO_2)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO)R^4$ and C_{0-6}alkylOR^4, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkyl-heteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3;

R^3 is selected from halogen, NO_2, CHO, C_{0-6}alkylCN, C_{0-6}alkylOR^4, C_{1-6}haloalkyl, C_{0-6}alkyl$N(R^4)_2$, $NR^4C(O)R^4$, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$CON(R^4)_2$, C_{0-6}alkyl$NR^4(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, $NR^4(CO)N(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, C_{0-6}alkylCOR^4, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)N(R^4)_2$, C_{0-6}alkylSR^4, C_{0-6}alkyl$(SO_2)N(R^4)_2$, OC_{2-6}alkyl-$NR^4(SO_2)R^4$, C_{0-6}alkyl$(SO)N(R^4)_2$, OSO_2R^4, SO_3R^4, C_{0-6}alkyl$NR^4(SO_2)N(R^4)_2$, C_{0-6}alkylN-$R^4(SO)R^4$, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkyl-C_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, and C_{0-6}alkylheterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkyl-heterocyclyl is optionally substituted with one or more R^6;

R^4 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{1-6}alkylOR^5, and C_{1-6}alkyl$N(R^5)_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkyl-heteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^4 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^5 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheterocyclyl and C_{0-6}alkylheteroaryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkyl-C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;

R^6 is selected from oxo, halogen, nitro, CN, OR^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylheterocyclyl, C_{1-6}haloalkyl, OC_{2-6}alkyl$N(R^7)_2$, $N(R^7)_2$, $CON(R^7)_2$, $NR^7(CO)R^7$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^7, $SON(R^7)_2$, $(SO_2)N(R^7)_2$, $NR^7SO_2R^7$, NR^7SOR^7, SO_2R^7, SOR^7, $(CO)C_{1-6}$alkyl$N(R^7)_2$, $(SO_2)C_{1-6}$alkyl$N(R^7)_2$, OSO_2R^7 and SO_3R^7, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, or C_{0-6}alkylC_{3-6}cycloalkyl is optionally substituted with one or more substituents selected from halo, nitro, cyano, OR^7, C_{1-6}alkyl, or C_{1-6}haloalkyl;

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_6cycloalkynyl, aryl, heteroaryl and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one to three substituents selected from hydroxy, cyano, halogen and OC_{1-3}alkyl; or two R^7 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring being optionally substituted with one or more substituents independently selected from hydroxy, OC_{1-3}alkyl, cyano and halogen.

In one embodiment of the present invention, A is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{0-6}alkylC_{3-8}cycloalkyl, C_{0-6}alkylC_{5-6}cycloalkenyl, or C_{0-6}alkyl-C_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;

B is aryl or heteroaryl; wherein said aryl or heteroaryl is optionally substituted with one or more R^2;

C is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)R^4$, C_{0-6}alkyl$NR^4(CO)R^4$, C_{0-6}alkylSR^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl,

C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{5-6}cycloalkenyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, C_{0-6}alkylOR^4, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)R^4$, C_{0-6}alkyl$NR^4(CO)R^4$, C_{0-6}alkylSR^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl or is optionally substituted with one or more R^3; or two R^1 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^2 is selected from C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)R^4$, C_{0-6}alkylSR^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, and C_{0-6}alkylOR^4, wherein said C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3,
or two R^2 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^3 is selected from halogen, NO_2, C_{0-6}alkylCN, C_{0-6}alkylOR^4, C_{1-6}haloalkyl, C_{0-6}alkyl$N(R^4)_2$, $NR^4C(O)R^4$, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$CON(R^4)_2$, C_{0-6}alkyl$NR^4(CO)R^4$, $O(CO)R^4$, C_{0-6}alkylCOR^4, C_{0-6}alkylSR^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, and C_{0-6}alkylheterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;

R^4 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{1-6}alkylOR^5, and C_{1-6}alkyl$N(R^5)_2$,

wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6; or two R^4 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^5 is selected from hydrogen, C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheterocyclyl and C_{0-6}alkylheteroaryl, wherein said C_{1-6}alkyl, C_{0-6}alkyl-C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^5 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^6 is selected from oxo, halogen, nitro, CN, OR^7, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylheterocyclyl, C_{1-6}haloalkyl, OC_{2-6}alkyl$N(R^7)_2$, $N(R^7)_2$, $CON(R^7)_2$, $NR^7(CO)R^7$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^7, SO_2R^7, SOR^7, wherein said C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl or C_{0-6}alkylC_{3-6}cycloalkyl is optionally substituted with one or more substituents independently selected from halo, nitro, cyano, OR^7, C_{1-6}alkyl, C_{1-3}haloalkyl, or OC_{1-3}haloalkyl;

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{3-6}cycloalkyl, aryl, heteroaryl and heterocyclyl, wherein said C_{1-6}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, cyano, halogen and OC_{1-3}alkyl; or two R^7 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring being optionally substituted with one or more substituents independently selected from hydroxy, OC_{1-3}alkyl, cyano and halogen.

In another embodiment of the present invention B is phenyl or heteroaryl.

In one embodiment, R^2 is C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, halogen, C_{0-6}alkylCN or C_{0-6}alkylOR^4.

In one embodiment, R^2 is fluoro, OR^4 or C_{1-6}alkyl.

In another embodiment of the present invention R^2 is halogen, such as fluoro, cyano or C_{0-6}alkylOR^4.

In another embodiment of the present invention R^2 is fluoro.

In one embodiment, R^4 is hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{0-6}alkylC_{3-6}cycloalkyl or C_{0-6}alkylheteroaryl.

In one embodiment, R^4 is hydrogen, C_{1-6}alkyl or C_{1-3}haloalkyl.

In another embodiment of the present invention R^4 is hydrogen.

In another embodiment of the present invention A is C_{1-6}alkyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{0-6}alkylC_{3-8}cycloalkyl, or C_{0-6}alkylC_{3-8}heterocyclyl.

In one embodiment, A is C_{0-6}alkylC_{3-8}cycloalkyl or C_{0-6}alkyl-C_{3-8}heterocyclyl.

In another embodiment of the present invention R^1 is C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkyl$N(R^4)_2$, C_{0-6}alkylOR^4, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, C_{0-6}alkyl$CON(R^4)_2$, C_{0-6}alkyl$NR^4(CO)R^4$, C_{0-6}alkylSR^4, C_{0-6}alkylSO_2R^4 or C_{0-6}alkylSOR^4.

In one embodiment, R^1 is C_{1-6}alkyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylOR^4, halogen, C_{0-6}alkylCN or C_{0-6}alkylCOR^4.

In one embodiment, R^1 is C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylOR^4, halogen or C_{0-6}alkylCOR^4.

In another embodiment of the present invention C_{1-6}alkyl is methyl or ethyl.

In another embodiment of the present invention C_{1-6}alkylaryl is CH_2-phenyl.

In another embodiment of the present invention C_{0-6}alkylC_{3-6}cycloalkyl is cyclohexyl.

In another embodiment of the present invention C_{0-6}alkylC_{3-8}heterocyclyl is piperidinyl.

In another embodiment of the present invention C_{0-6}alkylC_{3-8}heterocyclyl is tetrahydropyranyl.

In another embodiment of the present invention A is piperidinyl or cyclohexyl.

In one embodiment, C is hydrogen, C_{1-6}alkyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN or C_{0-6}alkyl$NR^4(CO)R^4$.

In another embodiment of the present invention C is selected from hydrogen, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylCN, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkyl$CON(R^4)_2$, C_{0-6}alkyl$NR^4(CO)R^4$.

In another embodiment of the present invention C is phenyl, pyridine or pyrimidine.

In another embodiment of the present invention R^3 is halogen, C_{0-6}alkylCN, C_{0-6}alkylOR^4, C_{1-6}haloalkyl, C_{1-6}alkyl.

In one embodiment, R^3 is halogen, NO_2, C_{0-6}alkylCN, C_{0-6}alkylOR^4, C_{1-6}haloalkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl or C_{0-6}alkylheterocyclyl.

In one embodiment, R^3 is halogen, C_{2-6}alkynyl, CN or OR^4.

In one embodiment, R^3 is halogen or C_{2-4}alkynyl.

In one embodiment, R^6 is oxo, halogen, CN, OR^7, C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl or C_{1-6}haloalkyl.

In one embodiment, R^6 is chloro.

In one embodiment of the present invention, A is C_{0-6}alkylC_{3-8}cycloalkyl or C_{0-6}alkyl-C_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;
B is aryl or heteroaryl; wherein said aryl or heteroaryl is optionally substituted with one or more R^2;
C is hydrogen, C_{1-6}alkyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkyl$NR^4(CO)R^4$;
R^1 is C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylOR^4, halogen or C_{0-6}alkylCOR^4;
R^2 is C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, halogen, C_{0-6}alkylCN or C_{0-6}alkylOR^4;
R^3 is halogen, C_{2-6}alkynyl, CN or OR^4;
R^4 is hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{0-6}alkylC_{3-6}cycloalkyl or C_{0-6}alkylheteroaryl;
R^6 is oxo, halogen, CN, OR^7, C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl or C_{1-6}haloalkyl.

In another embodiment of the present invention A is selected from C_{1-6}alkyl, C_{1-6}alkylaryl, C_{0-6}alkylC_{3-8}cycloalkyl and C_{0-6}alkylC_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;
B is aryl;
C is C_{0-6}alkylaryl or C_{0-6}alkylheteroaryl, wherein said C_{0-6}alkylaryl or C_{0-6}alkylheteroaryl is optionally substituted with one or more R^1;
R^1 C_{0-6}alkylCOR^4;
R^3 is C_{0-6}alkylOR^4; and
R^4 is C_{1-6}alkyl.

One embodiment of the present invention is a compound selected from

2-(3'-Methoxybiphenyl-3-yl)-2,5-dimethyl-2H-imidazol-4-amine;

(R)-2-(3'-Methoxybiphenyl-3-yl)-2,5-dimethyl-2H-imidazol-4-amine;

2,5-Dimethyl-2-(3-(pyridin-3-yl)phenyl)-2H-imidazol-4-amine;

2-Ethyl-5-methyl-2-(3-(pyridin-3-yl)phenyl)-2H-imidazol-4-amine;

2-Cyclohexyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine;

2-Cyclohexyl-5-methyl-2-(3-(pyridin-3-yl)phenyl)-2H-imidazol-4-amine;

2-(3'-Methoxybiphenyl-3-yl)-5-methyl-2-(tetrahydro-2H-pyran-4-yl)-2H-imidazol-4-amine;

1-(4-(4-Amino-2-(3'-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)piperidin-1-yl)ethanone;

2-Benzyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine; and

(R)-2-Benzyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine;

(R)- and (S)- 2-(2'-fluoro-3'-methoxybiphenyl-3-yl)-5-methyl-2-(pyridin-3-ylmethyl)-2H-imidazol-4-amine;

(R)- and (S)- 2-(3-(5-Chloropyridin-3-yl)phenyl)-5-methyl-2-(pyridin-3-ylmethyl)-2H-imidazol-4-amine;

2-(3-Bromophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine;

2-(3-(5-Chloropyridin-3-yl)phenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine;

2-Cyclopropyl-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-4-amine;

5-(4-Amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-3-methylpyridin-2(1H)-one;

5-(4-Amino-2-(3-(5-chloropyridin-3-yl)phenyl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;

5-(4-Amino-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;

5-(4-Amino-2-(3'-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;

5-(4-Amino-2-(3',5'-difluorobiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;

2-(3-(5-Chloropyridin-3-yl)-4-fluorophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine;

2-Cyclopropyl-2-(4-fluoro-3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-5-methyl-2H-imidazol-4-amine;

2-(3-(5-Chloropyridin-3-yl)phenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine;

2-(3-(5-Fluoropyridin-3-yl)phenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine;

2-(3-(5-Methoxypyridin-3-yl)phenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine;

2-(3'-Methoxybiphenyl-3-yl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine;

N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)phenyl)pyrazine-2-carboxamide;

2-(3-(5-Chloropyridin-3-yl)phenyl)-2-cyclobutyl-5-methyl-2H-imidazol-4-amine;

2-Cyclobutyl-2-(3-(5-fluoropyridin-3-yl)phenyl)-5-methyl-2H-imidazol-4-amine;

2-Cyclobutyl-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-4-amine;

2-(3-(5-Chloropyridin-3-yl)phenyl)-2-isopropyl-5-methyl-2H-imidazol-4-amine;

2-(3-(5-Fluoropyridin-3-yl)phenyl)-2-isopropyl-5-methyl-2H-imidazol-4-amine;

2-Isopropyl-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-4-amine;

2-Cyclohexyl-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine;

2-Cycloheptyl-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine;

2-(Bicyclo[2.2.1]heptan-2-yl)-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine;

2-Cyclooctyl-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine;

2-(4-Methoxyphenyl)-5-methyl-2-(3-phenylpropyl)-2H-imidazol-4-amine;

2-(4-Methoxyphenyl)-2-(3-(3-methoxyphenyl)propyl)-5-methyl-2H-imidazol-4-amine;

5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2'-fluoro-5'-methoxybiphenyl-2-ol;

5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-5'-chloro-2'-fluorobiphenyl-2-ol;

5'-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-6-fluoro-2'-hydroxybiphenyl-3-carbonitrile;

5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2'-fluoro-3'-methoxybiphenyl-2-ol;

4-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(5-(prop-1-ynyl)pyridin-3-yl)phenol;

4-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(pyrazin-2-yl)phenol;
4-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(4-(prop-1-ynyl)pyridin-2-yl)phenol;
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2',5'-dichlorobiphenyl-2-ol;
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2'-chloro-5'-methoxybiphenyl-2-ol;
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-4-fluorophenyl)-5-chloropicolinamide;
3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-N-(3-chlorophenyl)benzamide;
3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-N-(4-chlorophenyl)benzamide;
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)phenyl)-4-chloropicolinamide;
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)phenyl)-5-chloropicolinamide;
5-(4-Amino-5-methyl-2-(3'-(prop-1-ynyl)biphenyl-3-yl)-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;
5-(4-Amino-2-(2'-fluoro-5'-(prop-1-ynyl)biphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;
as a free base or a pharmaceutically acceptable salt thereof.

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).

The compounds of the formula (I) may be administered in the form of a prodrug which is broken down in the human or animal body to give a compound of the formula (I). Examples of prodrugs include in vivo hydrolysable esters of a compound of the formula (I). An in vivo hydrolysable (or cleavable) ester of a compound of the formula (I) that contains a carboxy or a hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Various forms of prodrugs are known in the art.

The definitions set forth in this application are intended to clarify terms used throughout this application. The term "herein" means the entire application.

A variety of compounds in the present invention may exist in particular geometric or stereoisomeric forms. The present invention takes into account all such compounds, including tautomers, cis- and trans isomers, R- and S- enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as being covered within the scope of this invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention. The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms, by synthesis from optically active starting materials, or synthesis using optically active reagents. When required, separation of the racemic material can be achieved by methods known in the art. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents, positions of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used in this application, the term "optionally substituted," means that substitution is optional and therefore it is possible for the designated atom or moiety to be unsubstituted.

As used herein, "alkyl", used alone or as a suffix or prefix, is intended to include both branched and straight chain saturated aliphatic hydrocarbon groups having from 1 to 12 carbon atoms or if a specified number of carbon atoms is provided then that specific number would be intended. For example "C_{0-6} alkyl" denotes alkyl having 0, 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl. In the case where a subscript is the integer 0 (zero) the group to which the subscript refers to indicates that the group may be absent, i.e. there is a direct bond between the groups.

As used herein, "alkenyl" used alone or as a suffix or prefix is intended to include both branched and straight-chain alkene or olefin containing aliphatic hydrocarbon groups having from 2 to 12 carbon atoms or if a specified number of carbon atoms is provided then that specific number would be intended. For example "C_{2-6}alkenyl" denotes alkenyl having 2, 3, 4, 5 or 6 carbon atoms. Examples of alkenyl include, but are not limited to, vinyl, allyl, 1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl.

As used herein, "alkynyl" used alone or as a suffix or prefix is intended to include to include both branched and straight-chain alkynyl or olefin containing aliphatic hydrocarbon groups having from 2 to 12 carbon atoms or if a specified number of carbon atoms is provided then that specific number would be intended. For example ethynyl, propynyl (e.g. 1-propynyl, 2-propynyl), 3-butynyl, pentynyl, hexynyl and 1-methylpent-2-ynyl.

As used herein, "aromatic" refers to hydrocarbonyl groups having one or more unsaturated carbon ring(s) having aromatic characters, (e.g. 4n + 2 delocalized electrons) and comprising up to 14 carbon atoms. In addition "heteroaromatic" refers to groups having one or more unsaturated rings containing carbon and one or more heteroatoms such as nitrogen, oxygen or sulphur having aromatic character (e.g. 4n + 2 delocalized electrons).

As used herein, the term "aryl" refers to an aromatic ring structure made up of from 5 to 14 carbon atoms. Ring structures containing 5, 6, 7 and 8 carbon atoms would be single-ring aromatic groups, for example, phenyl. Ring structures containing 8, 9, 10, 11, 12, 13, or 14 would be polycyclic, for example naphthyl. The aromatic ring can be substituted at one or more ring positions with such substituents as described above. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, for example, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls. Examples of polycyclic rings include, but are not limited to, 2,3-dihydro-1,4-benzodioxine and 2,3-dihydro-1-benzofuran.

As used herein, the terms "cycloalkyl" or "carbocyclyl" are intended to include saturated ring groups, having the specified number of carbon atoms. These may include fused or bridged polycyclic systems. Preferred cycloalkyls have from 3 to 10 carbon atoms in their ring structure, and more preferably have 3, 4, 5, and 6 carbons in the ring structure. For example, "C_{3-6} cycloalkyl" denotes such groups as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, the term "cycloalkenyl" is intended to include unsaturated ring groups, having the specified number of carbon atoms. These may include fused or bridged polycyclic systems. Preferred cycloalkenyls have from 3 to 10 carbon atoms in their ring structure, and more preferably have 3, 4, 5, and 6 carbons in the ring structure. For example, "C_{3-6} cycloalkenyl" denotes such groups as cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo.

"Counterion" is used to represent a small, negatively or positively charged species such as chloride, bromide, hydroxide, acetate, sulfate, tosylate, benezensulfonate, ammonium, lithium ion and sodium ion and the like.

As used herein, the term "heterocyclyl" or "heterocyclic" or "heterocycle" refers to a saturated, unsaturated or partially saturated, monocyclic, bicyclic or tricyclic ring (unless otherwise stated) containing 3 to 20 atoms of which 1, 2, 3, 4 or 5 ring atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group is optionally be replaced by a -C(O)-; and where unless stated to the contrary a ring nitrogen or sulphur atom is optionally oxidised to form the N-oxide or S-oxide(s) or a ring nitrogen is optionally quarternized; wherein a ring –NH is optionally substituted with acetyl, formyl, methyl or mesyl; and a ring is optionally substituted with one or more halo. It is understood that when the total number of S and O atoms in the heterocyclyl exceeds 1, then these heteroatoms are not adjacent to one another. If the said heterocyclyl group is bi- or tricyclic then at least one of the rings may optionally be a heteroaromatic or aromatic ring provided that at least one of the rings is non-heteroaromatic. If the said heterocyclyl group is monocyclic then it must not be aromatic. Examples of heterocyclyls include, but are not limited to, piperidinyl, *N*-acetylpiperidinyl, *N*-methylpiperidinyl, *N*-formylpiperazinyl, *N*-mesylpiperazinyl, homopiperazinyl, piperazinyl, azetidinyl, oxetanyl, morpholinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl, tetrahydropyranyl, dihydro-*2H*-pyranyl, tetrahydrofuranyl, tetrahydro-thiopyranyl, tetrahydro-thiopyran 1-oxide, tetrahydro-thiopyran 1,1-dioxide,1H-pyridin-2-one, and 2,5-dioxoimidazolidinyl.

As used herein, "heteroaryl" refers to a heteroaromatic 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, benzimidazolyl, benzoxazolyl, aza-benzoxazolyl imidazothiazolyl, benzo[1,4]dioxinyl, benzo[1,3]dioxolyl and the like. In some embodiments, the heteroaryl group has from 1 to 20 carbon atoms, and in further embodiments from 3 to 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to 14, 4 to 14, 3 to 7, or 5 to 6 ring-forming atoms. In some embodiments, the

heteroaryl group has 1 to 4, 1 to 3, or 1 to 2 heteroatoms. In some embodiments, the heteroaryl group has 1 heteroatom.

As used herein, "haloalkyl", used alone or as a suffix or prefix, is intended to include both branched and straight chain saturated aliphatic hydrocarbon groups, having at least one halogen substituent and having from 1 to 12 carbon atoms or if a specified number of carbon atoms is provided then that specific number would be intended. For example "C_{0-6}haloalkyl" denotes alkyl having 0, 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, 1-fluoroethyl, 3-fluoropropyl, 2-chloropropyl, 3,4-difluorobutyl.

As used herein, the phrase "protecting group" means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999).

As used herein, "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such non-toxic salts include those derived from inorganic acids such as hydrochloric acid.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like diethyl ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.

The present invention further includes all tautomeric forms of compounds of the invention. As used herein, "tautomer" means other structural isomers that exist in equilibrium resulting from the migration of a hydrogen atom. For example, keto-enol tautomerism where the resulting compound has the properties of both a ketone and an unsaturated alcohol. Other examples of tautomerism include 2H-imidazole-4-amine and its tautomer 1,2-dihydroimidazol-5-imine, and 2H-imidazol-4-thiol and its tautomer 1,2-dihydroimidazol-5-thione. It is understood that in compound representations throughout this description, only one of the possible tautomers of the compound is drawn or named.

As used herein "stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

Compounds of the invention further include hydrates and solvates.

The present invention further includes isotopically-labelled compounds of the invention. An "isotopically" or "radio-labelled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide that is incorporated in the instant

radio-labelled compounds will depend on the specific application of that radio-labelled compound. For example, for *in vitro* receptor labelling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I , ^{131}I, ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

It is understood that a "radio-labelled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I , ^{35}S and ^{82}Br.

Compounds of the present invention may be administered orally, parenteral, buccal, vaginal, rectal, inhalation, insufflation, sublingually, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

The quantity of the compound to be administered will vary for the patient being treated and will vary from about 100 ng/kg of body weight to 100 mg/kg of body weight per day. For instance, dosages can be readily ascertained by those skilled in the art from this disclosure and the knowledge in the art. Thus, the skilled artisan can readily determine the amount of compound and optional additives, vehicles, and/or carrier in compositions and to be administered in methods of the invention.

In another aspect of the invention, there is provided that the compounds of the invention, or a pharmaceutically acceptable salt thereof, can be used as medicaments, e.g. to treat or prevent Aβ-related pathologies.

In another aspect of the invention, there is provided that the compounds of the invention, or a pharmaceutically acceptable salt thereof, can be used for the manufacture of a medicament to treat or prevent Aβ-related pathologies.

In another aspect of the invention, there is provided a method for the treatment of Aβ-related pathologies, comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to a subject, such as a mammal or a human being, in need thereof.

The compounds of the invention and their pharmaceutically acceptable salts thereby provides methods of treatment of Aβ-related pathologies, such as, but not limited to, Alzheimer's disease, Downs syndrome, β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, a disorder associated with cognitive impairment, MCI ("mild cognitive impairment"), memory loss, attention deficit symptoms associated with Alzheimer's disease, neurodegeneration associated with Alzheimer's disease, dementia of mixed vascular origin, dementia of degenerative origin, pre-senile dementia, senile dementia, dementia associated with Parkinson's disease, progressive supranuclear palsy traumatic brain injury and cortical basal degeneration.

In another aspect of the invention, there is provided a pharmaceutical composition comprising as active ingredient a therapeutically effective amount of a compound according formula (I) in association with pharmaceutically acceptable excipients, carriers or diluents.

In another aspect of the invention, there is provided a method of inhibiting activity of BACE with a compound according to formula (I).

In another aspect of the invention, there is provided a method of treating or preventing an Aβ-related pathology in a mammal, such as a human being , comprising administering to said patient a therapeutically effective amount of a compound according to formula (I), and at least one cognitive enhancing agent, memory enhancing agent, or choline esterase inhibitor, wherein said Aβ-related pathology is Alzheimer Disease.

The treatment of Aβ-related pathology defined herein may be applied as a mono therapy or may involve, in addition to the compound of the invention, conjoint treatment with conventional therapy of value in treating one or more disease conditions referred to herein. Such conventional therapy may include one or more of the following categories of agents: acetyl cholinesterase inhibitors, anti-inflammatory agents, cognitive and/or memory enhancing agents or atypical antipsychotic agents. Cognitive enhancing agents, memory enhancing agents and acetyl choline esterase inhibitors includes, but not limited to, donepezil (Aricept), galantamine (Reminyl or Razadyne), rivastigmine (Exelon), tacrine (Cognex) and memantine (Namenda, Axura or Ebixa). Atypical antipsychotic agents includes, but not limited to, olanzapine (marketed as Zyprexa), aripiprazole (marketed as Abilify), risperidone (marketed as Risperdal), quetiapine (marketed as Seroquel), clozapine (marketed as Clozaril), ziprasidone (marketed as Geodon) and olanzapine/fluoxetine (marketed as Symbyax).

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of the invention.

Additional conventional therapy may include one or more of the following categories of agents:

(i) antidepressants such as agomelatine, amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin duloxetine, elzasonan, escitalopram, fluvoxamine, fluoxetine, gepirone, imipramine, ipsapirone, maprotiline, nortriptyline, nefazodone, paroxetine, phenelzine, protriptyline, ramelteon, reboxetine, robalzotan, sertraline, sibutramine, thionisoxetine, tranylcypromaine, trazodone, trimipramine, venlafaxine and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(ii) atypical antipsychotics including for example quetiapine and pharmaceutically active isomer(s) and metabolite(s) thereof.

(iii) antipsychotics including for example amisulpride, aripiprazole, asenapine, benzisoxidil, bifeprunox, carbamazepine, clozapine, chlorpromazine, debenzapine, divalproex, duloxetine, eszopiclone, haloperidol, iloperidone, lamotrigine, loxapine, mesoridazine, olanzapine, paliperidone, perlapine, perphenazine, phenothiazine, phenylbutylpiperidine, pimozide, prochlorperazine, risperidone, sertindole, sulpiride, suproclone, suriclone, thioridazine, trifluoperazine, trimetozine, valproate, valproic acid, zopiclone, zotepine, ziprasidone and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(iv) anxiolytics including for example alnespirone, azapirones,benzodiazepines, barbiturates such as adinazolam, alprazolam, balezepam, bentazepam, bromazepam, brotizolam, buspirone, clonazepam, clorazepate, chlordiazepoxide, cyprazepam, diazepam, diphenhydramine, estazolam, fenobam, flunitrazepam, flurazepam, fosazepam, lorazepam, lormetazepam, meprobamate, midazolam, nitrazepam, oxazepam, prazepam, quazepam, reclazepam, tracazolate, trepipam, temazepam, triazolam, uldazepam, zolazepam and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(v) anticonvulsants including for example carbamazepine, clonazepam, ethosuximide, felbamate, fosphenytoin, gabapentin, lacosamide, lamotrogine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabaline, rufinamide, topiramate, valproate, vigabatrine, zonisamide and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(vi) Alzheimer's therapies including for example donepezil, rivastigmine, galantamine, memantine, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(vii) Parkinson's therapies including for example deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(viii) migraine therapies including for example almotriptan, amantadine, bromocriptine, butalbital, cabergoline, dichloralphenazone, dihydroergotamine, eletriptan, frovatriptan, lisuride, naratriptan, pergolide, pizotiphen, pramipexole, rizatriptan, ropinirole, sumatriptan, zolmitriptan, zomitriptan, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(ix) stroke therapies including for example thrombolytic therapy with eg activase and desmoteplase, abciximab, citicoline, clopidogrel, eptifibatide, minocycline, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(x) urinary incontinence therapies including for example darafenacin, falvoxate, oxybutynin, propiverine, robalzotan, solifenacin, tolterodine and and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(xi) neuropathic pain therapies including for example lidocain, capsaicin, and anticonvulsants such as gabapentin, pregabalin, and antidepressants such as duloxetine, venlafaxine, amitriptyline, klomipramine, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(xii) nociceptive pain therapies such as paracetamol, NSAIDS and coxibs, such as celecoxib, etoricoxib, lumiracoxib, valdecoxib, parecoxib, diclofenac, loxoprofen, naproxen, ketoprofen, ibuprofen, nabumeton, meloxicam, piroxicam and opioids such as morphine, oxycodone, buprenorfin, tramadol, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(xiii) insomnia therapies including for example agomelatine, allobarbital, alonimid, amobarbital, benzoctamine, butabarbital, capuride, chloral, cloperidone, clorethate, dexclamol, ethchlorvynol, etomidate, glutethimide, halazepam, hydroxyzine, mecloqualone, melatonin, mephobarbital, methaqualone, midaflur, nisobamate, pentobarbital, phenobarbital, propofol, ramelteon, roletamide, triclofos, secobarbital,

zaleplon, zolpidem and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(xiv) mood stabilizers including for example carbamazepine, divalproex, gabapentin, lamotrigine, lithium, olanzapine, quetiapine, valproate, valproic acid, verapamil, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

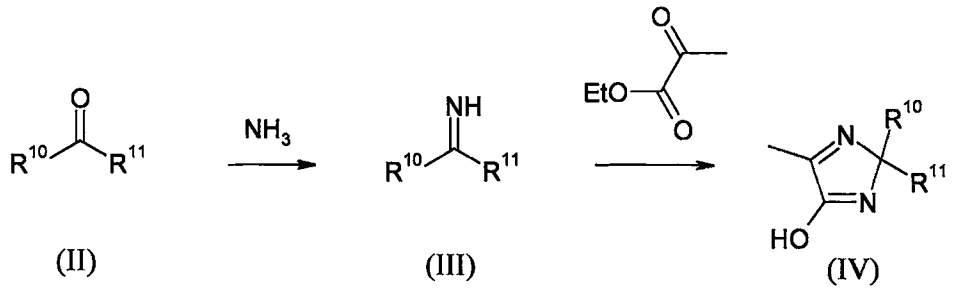
Such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active compound or compounds within approved dosage ranges and/or the dosage described in the publication reference.

Methods of preparation

The present invention also relates to processes for preparing the compound of formula (I) as a free base or a pharmaceutically acceptable salt thereof. Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are for example described in *Protective Groups in Organic Synthesis* by T.W. Greene, P.G.M Wutz, 3rd Edition, Wiley-Interscience, New York, 1999. It is understood that microwaves can alternatively be used for the heating of reaction mixtures.

Another aspect of the present invention provides a process for preparing a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein, unless specified otherwise, A, B and C are defined as in formula (I) above, R^C is defined as for C in formula (I) above and R^1 is, unless specified otherwise, as defined in formula (I); R^{10} and R^{11} are defined as A or B above, or may be defined as groups that can be converted to A or B in subsequent transformations, R^{12} may be defined as R^4 above, and LG represents a leaving group such as halogen (such as chlorine, bromine or iodine) or an alkyl-, aryl- or haloalkyl-sulfonate (such as triflate). A compound of formula (VI) may be equivalent to a compound of formula (I). Said process comprises of:

(i) Formation of a corresponding compound of formula (IV):

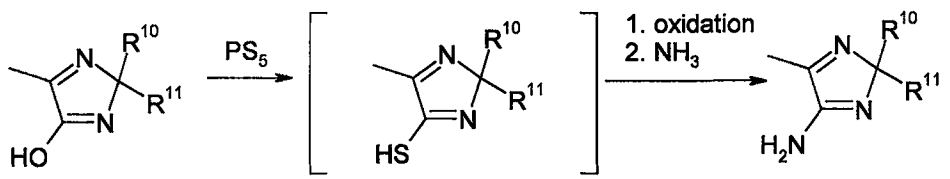


(II) (III) (IV)

Scheme 1

A ketone of formula (II), is reacted with ammonia to form intermediate (III), (*Scheme 1*). The compound of formula (III) is further reacted with ethyl 2-oxopropanoate to form an imidazole compound of formula (IV). Said reaction may be performed at a temperature range between +100 °C and +160 °C, in a suitable solvent, such as methanol, ethanol or isopropyl alcohol.

(ii) Formation of a corresponding compound of formula (VI):

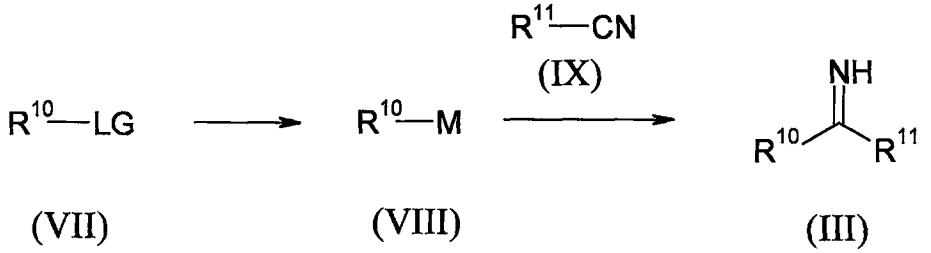


(IV) (V) (VI)

Scheme 2

The amino imidazole compound (VI) may be obtained by an initial formation of intermediate (V), by reacting the alcohol of formula (IV), with a sulphurating reagent such as phosphorus pentasulfide in the presence of a base such as pyridine. The transformation to a compound of formula (VI) may be performed by reacting the intermediate of formula (V) with ammonia, optionally in the presence of an oxidation agent, such as tert-butyl hydroperoxide.

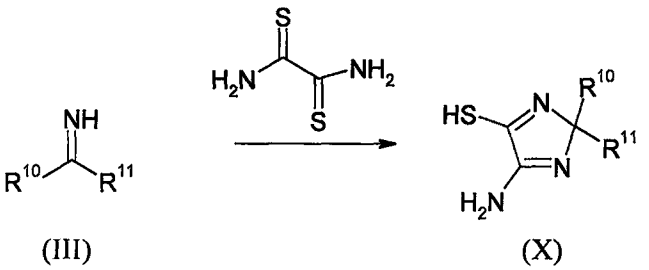
(iii) Formation of a corresponding compound of formula (III):



Scheme 3

A compound of formula (III), may be obtained, as shown in (*Scheme 3*), by reacting compound of formula (VII), wherein LG is defined as above, with an organometallic reagent such as an alkyl lithium as for example butyl lithium, or with a metal such as magnesium, to form an intermediate compound of formula (VIII), wherein M is a metal, such as for example lithium or MgX, wherein X is a halide such as bromo or chloro. The compound of formula (VIII) is further reacted with a nitrile of formula (IX). Said reaction may be performed at a temperature range between -78 °C and room temperature, in a suitable solvent such as THF, 2-methyl-tetrahydrofuran or diethyl ether. A catalyst such as CuBr may facilitate the reaction.

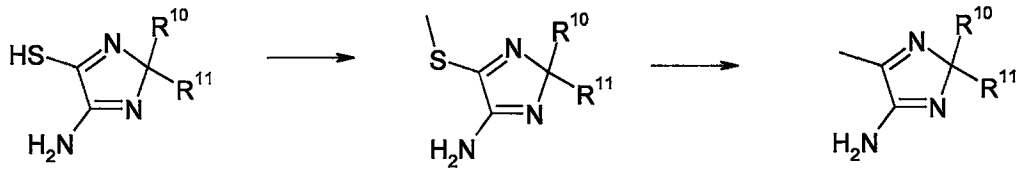
(iv) Formation of a corresponding compound of formula (X):



Scheme 4

An imine of formula (III), is reacted with ethanebis(thioamide) to form a compound of formula (X) (*Scheme 4*). Said reaction may be performed at a temperature range between +120 °C and +180 °C, in a suitable solvent, such as methanol, ethanol or isopropyl alcohol.

(v) Formation of a corresponding compound of formula (VI):

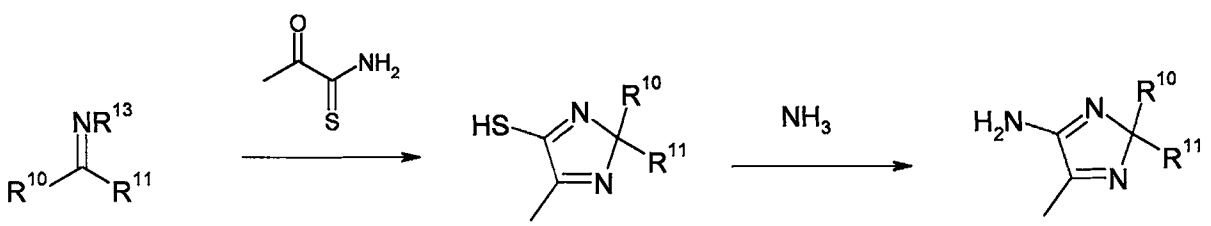


(X) (XI) (VI)

Scheme 5

An alkylating agent, such as methyl iodide and a thioimidazole of formula (X) are reacted to form a compound of formula (XI) (*Scheme 5*). Said compound (XI) may be further transformed into a compound of formula (VI) by reacting it with an organometallic reagent, such as methylmagnesium bromide in the presence of a suitable catalyst, such as [1,3-bis(diphenylphosphino)propane]nickel(II) chloride. Alternatively, the compound of formula (VI) may also be obtained by reacting compound of formula (XI) with a mixture of zinc iodide and methylmagnesium bromide in the presence of a suitable catalyst such as bis(triphenylphosphine)palladium(II) chloride in a suitable solvent such as THF, 2-methyl-tetrahydrofuran or toluene.

(vi) Formation of a corresponding compound of formula (VI):



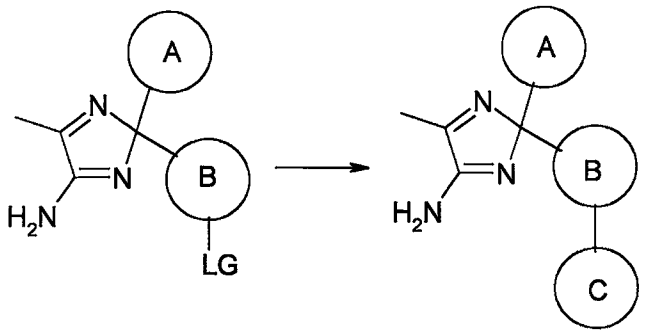
(III) (V) (VI)

Scheme 6

A compound of formula (VI) may be obtained from a compound of formula (III), wherein R^{13} is hydrogen, S(O)alkyl, C(O)alkyl, $S(O)_2$alkyl, OH or Oalkyl (Scheme 6). Compound (III) may optionally be coordinated to a Lewis acid, as for example BF_3, $AlCl_3$, or $TiCl_4$, to facilitate the reaction. An imine of formula (III) is reacted with 2-oxopropane thioamide (described in Asinger et al. *Justus Liebigs Annalen der Chemie* **1971,** vol 744, p. 51-64) in a solvent such as methanol at a temperature between room temperature and reflux temperature to yield a compound of formula (V). The compound of formula (V) is subsequently treated with ammonia, in a suitable solvent such as methanol, THF, or 2-

methyl-tetrahydrofuran, optionally in the presence of an oxidation agent, such as tert-butyl hydroperoxide, at a temperature between room temeprature and 150 °C, optionally in a closed system, to yield the compound of formula (VI).

(vii) Formation of a corresponding compound of formula (I):



(XII) (I)

Scheme 7

A compound of formula (I) may be obtained (*Scheme 7*) by starting from, for example, a compound of formula (XII), and reacting said compound of formula (XII) with a boronic acid or a boronic ester or a stannane of formula T-R^C, wherein T is for example $B(OH)_2$, $B(Oalkyl)_2$, or SnR_3, and R^C is as defined above, in the presence of a transition metal catalyst such as a palladium catalyst, such as [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride, tetrakis(triphenylphosphine)-palladium(0), palladium diphenylphosphineferrocene dichloride, palladium(II) acetate or bis(dibenzylideneacetone) palladium (0). Optionally, a suitable ligand such as triphenylphosphine, tri-*tert*-butylphosphine or 2-(dicyclohexylphosphino)biphenyl, or zinc and sodium triphenylphosphinetrimetasulfonate, is used. A suitable base, such as cesium fluoride, an alkyl amine, such as triethyl amine, or an alkali metal or alkaline earth metal carbonate or hydroxide such as potassium carbonate, sodium carbonate, cesium carbonate, or sodium hydroxide, may be used in the reaction. Said reaction may be performed in a suitable solvent, such as toluene, tetrahydrofuran, 2-methyl-tetrahydrofuran, dioxane, dimethoxyethane, water, ethanol, *N,N*-dimethylacetamide, acetonitrile or *N,N*-dimethylformamide, or mixtures thereof.

(viii) Formation of a corresponding compound of formula (I):

A compound of formula (I), wherein C is cyano, may be obtained (*Scheme 7*) by starting from, for example, a compound of formula (XII), wherein LG is a leaving group such as a halogen, (such as iodide, bromide or chlorine), and reacting said compound of formula (XII) with a a metal cyano reagent such as copper(I) cyanide.

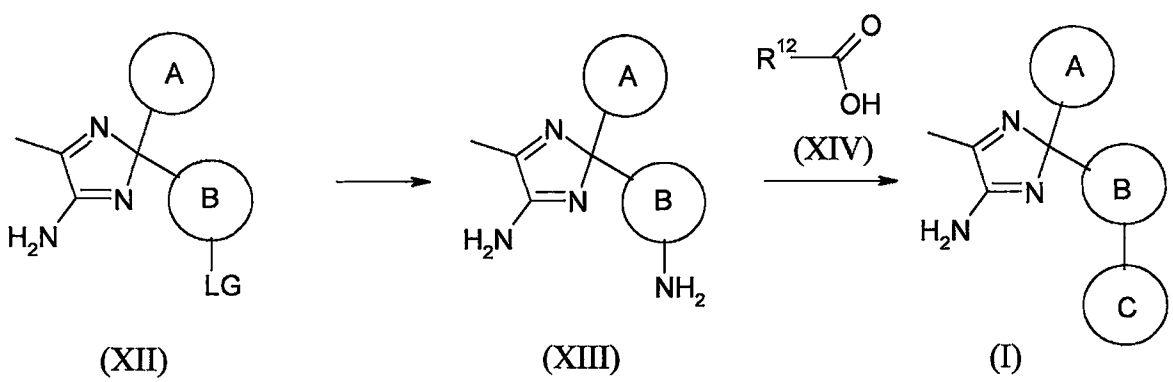
(ix) Formation of a corresponding compound of formula (I):

A compound of formula (I), wherein C is an alkyl group such as methyl may be generated from compound of formula (XII) (*Scheme 7*), wherein LG represents a leaving group, such as a halogen, (such as iodide, bromide or chlorine), by reaction with an organometallic reagent generated from zinc iodide and methylmagnesium bromide under the influence of a transition metal catalyst such as for example bis(triphenylphosphine)palladium(II) chloride.

(x) Formation of a corresponding compound of formula (I):

A compound of formula (I) wherein C is $NHC(O)R^{12}$ may be prepared according to Scheme 7 by reacting a compound of formula (XII) with a compound $R^{12}C(O)NH_2$ in the presence of a suitable palladium catalyst such as palladium(II) acetate, optionally in the presence of a suitable ligand such as Xantphos. Said reaction is preformed in the presence of a suitable base such as cesium carbonate in a suitable solvent such as THF or 2-methyl-tetrahydrofuran at a temperature between 100 °C to 160 °C.

Alternatively a compound of formula (I) wherein C is $NHC(O)R^{12}$ may be obtained from a compound of formula (XII) as shown in Scheme 8.



Scheme 8

A compound of formula (XII) is reacted with ammonia in the presence of trans-4-hydroxy-L-proline, potassium carbonate and copper(I)iodide in a solvent such as DMSO at a temperature between room temperature and 150 °C to give a compound of formula (XIII). Said compound of formula (XIII) is further reacted with an acid of formula (XIV) in the presence of an amide coupling agent such as 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide in a solvent such as DMF, optionally in the presence of hydrochloric acid.

Compounds of formula (II), (III), (VII), (IX), or (XIV) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

General Methods

All solvents used were of analytical grade and commercially available anhydrous solvents were routinely used for reactions. Starting materials used were available from commercial sources, or prepared according to literature procedures. Room temperature refers to 20 – 25 °C. Solvent mixture compositions are given as volume percentages or volume ratios.

Microwave heating was performed in a Biotage Creator, Initiator or Smith Synthesizer Single-mode microwave cavity producing continuous irradiation at 2450 MHz. It is understood that microwaves can be used for the heating of reaction mixtures.

Thin layer chromatography (TLC) was performed on Merck TLC-plates (Silica gel 60 F_{254}) and and spots were UV visualized. Flash chromatography was performed on a Combi Flash® Companion™ using RediSep™ normal-phase flash columns. Straight phase flash column chromatography was manually performed on Merck Silica gel 60 (0.040-0.063mm), or automatically using an ISCO Combiflash® Companion™ system using the solvent system indicated. Phase separation was optionally performed on an Isolute® phase separator.

^{1}H NMR spectra were recorded in the indicated deuterated solvent at 400 MHz unless otherwise indicated. Spectra were obtained using a Bruker av400 NMR spectrometer

operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C equipped with a 3 mm flow injection SEI $^{1}H/D$-^{13}C probe head with Z-gradients, using a BEST 215 liquid handler for sample injection, or using a Bruker DPX400 NMR spectrometer operating at 400 MHz for ^{1}H, 376 MHz for ^{19}F, and 100 MHz for ^{13}C, equipped with a 4-nucleus probehead with Z-gradients. 500 MHz spectra were recorded using a Bruker 500MHz Avance III NMR spectrometer, operating at 500 MHz for ^{1}H, 125 MHz for ^{13}C, and 50 MHz for ^{15}N equipped with a 5mm TXI probehead with Z-gradients. 600 MHz spectra were recorded using a Bruker DRX600 NMR spectrometer, operating at 600 MHz for ^{1}H, 150 MHz for ^{13}C, and 60 MHz for ^{15}N equipped with a 5mm TXI (or BBO) probehead with Z-gradients. Chemical shifts are given in ppm down- and upfield from TMS (0.00 ppm). The following reference signals were used: TMS δ 0.00, or the residual solvent signal of DMSO-d_6 δ 2.49, CD_3OD δ 3.30, acetone-d_6 2.04 or $CDCl_3$ δ 7.25 (unless otherwise indicated). Resonance multiplicities are denoted s, d, t, q, m, br and app for singlet, doublet, triplet, quartet, multiplet, broad and apparent, respectively. In some cases only diagnostic signals are reported.

HPLC analyses were performed on an Agilent HP1100 system consisting of a G1322A Micro Vacuum Degasser, a G1311A Quaternary Pump, a G1367 Well-Plate Autosampler, a G1316A Thermostatted Column Compartment and a G1315A Diode Array Detector. The column used was an Xbridge C8 30x50mm, 3.5µm or a Gemini C18, 3.0 x 50 mm, 3.0 µm, 110 Å run at a flow rate of 1.0 ml/min. Alternatively, HPLC analyses were performed on an Agilent HP1100 system consisting of a G1379A Micro Vacuum Degasser, a G1312A Binary Pump, a G1367 Well-Plate Autosampler, a G1316A Column Compartment and a G1315B Diode Array Detector. The column used was an Xbridge C8 30x50mm, 3.5µm or a Gemini C18, 3.0 x 50 mm, 3.0 µm, 110 Å run at a flow rate of 1.0 ml/min. Alternatively, HPLC analyses were performed on an Agilent HP1100 system consisting of a G1322A Micro Vacuum Degasser, a G1312A Binary Pump, a G1367 Well-Plate Autosampler, a G1316A Thermostatted Column Compartment and a G1315A Diode Array Detector. The column used was an Xbridge C8 30x50mm, 3.5µm or a Gemini C18, 3.0 x 50 mm, 3.0 µm, 110 Å run at a flow rate of 1.0 ml/min.

GC analyses were performed on a HP 6890 GC equipped with a G1512AX flame ionization detector supplied by Agilent Technologies. The column used was DB-5 MS, ID

0.18 mm x 10m, 0.18 μm (J&W Scientific). A linear temperature gradient was typically applied. Chiral GC analyses were performed on an HP 6890 GC equipped with a flame ionization detector supplied by Agilent Technologies. The column used was a Cyclodex B ID 0.25 mm x 30 m, 0.25 μm (Agilent Technologies). The temperature of the GC oven was typically held isocratically at for example 100 °C for 30 minutes.

Mass spectra (MS) were run using an automated system with atmospheric pressure chemical (APCI or CI) or electrospray (+ESI) ionization. Generally, only spectra where parent masses are observed are reported. The lowest mass major ion is reported for molecules where isotope splitting results in multiple mass spectral peaks (for example when chlorine is present). UPLC-MS analyses were performed on a Waters Acquity UPLC system consisting of an Acquity Autosampler, Acquity Sample Organizer, Acquity Column Manager, Acquity Binary Solvent Manager, Acquity UPLC PDA detector and a Waters 3100 Mass Spectrometer. The mass spectrometer was equipped with an electrospray ion source (ES) operated in positive and negative ion mode. Separation was performed on an Acquity column, UPLC BEH, C18 1.7 μM run at a flow rate of 0.5 ml/min. Alternatively, UPLCMS analyses were performed on a Waters Acquity UPLC system consisting of an Acquity Solvent Manager, Acquity Sample Organizer, Acquity Column Manager, Acquity Binary Solvent Manager, Acquity PDA detector and a Waters SQ Detector. The mass spectrometer was equipped with an electrospray ion source (ES) operated in positive and negative ion mode. Separation was performed on an Acquity column, UPLC BEH, C18 1.7 μM run at a flow rate of 0.5 ml/min.

LC-MS analyses were performed on an LC-MS system consisting of a Waters Alliance 2795 HPLC, a Waters PDA 2996 diode array detector, a Sedex 75 ELS detector and a ZQ 2000 single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ES) operated in positive and negative ion mode. Separation was performed on a Xbridge C18, 30x50mm, 3.5μm column or on a Gemini C18 3.0 x 50, 3 μm (Phenomenex) column run at a flow rate of 1 ml/min. Alternatively, LC-MS analyses were performed on an LC-MS consisting of a Waters sample manager 2777C, a Waters 1525μ binary pump, a Waters 1500 column oven, a Waters ZQ single quadrupole mass spectrometer, a Waters PDA2996 diode array detector and a Sedex 85 ELS detector. The

mass spectrometer was equipped with an electrospray ion source (ES) operated in positive and negative ion mode. The column used was a Xbridge C18, 30x50mm, 3.5μm or a Gemini C18, 3.0 mm x 50 mm, 3 μm, (Phenomenex) which was run at a flow rate of 1 ml/min. Alternatively, LC-MS analyses were performed on a LC-MS consisting of a Waters sample manager 2777C, a Waters 1525 μ binary pump, a Waters 1500 column oven, a Waters ZQ single quadrupole mass spectrometer, a Waters PDA2996 diode array detector and a Sedex 85 ELS detector. The mass spectrometer was configured with an atmospheric pressure chemical ionisation (APCI) ion source which was further equipped with atmospheric pressure photo ionisation (APPI) device. The mass spectrometer operated in positive and negative ion mode, switching between APCI and APPI mode. Separation was performed using a Gemini column C18, 3.0 mm x 50 mm, 3 μm, (Phenomenex) and run at a flow rate of 0.8 ml/min. Typical mobile phase systems for HPLC, UPLC-MS, and LCMS consisted of A: 10mM NH_4OAc (aq.) in 5% CH_3OH) or 10mM NH_4OAc in 5% CH_3CN and B: CH_3OH or CH_3CN and linear gradients from 100% A to 100% B was typically applied.

GCMS analysis was performed on a GC/DIP-MS system supplied by Agilent Technologies. The system consisted of a GC 6890N, G1530N, a G2614A Auto-sampler, G2613A injector and a G2589N mass spectrometer. The mass spectrometer was equipped with a Direct Inlet Probe (DIP) interface manufactured by SIM GmbH. 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* 50-550 and the scan speed was set to 2.91 scan/s. The sample solution was either injected on the GC or introduced by direct inlet to the probe tip. The GC column used was a DB-5 MS, ID 0.18 mm x 10m, 0.18 μm (J&W Scientific) or a VF-5 MS, ID 0.25 mm x 15m, 0.25 μm (Varian Inc.). A linear temperature gradient was typically applied. Alternatively, GCMS analysis was performed on a GC-MS system supplied by Agilent Technologies, consisting of a 6890N G1530N GC, a G2614A Auto-sampler, G2613A injector and a G2589N mass spectrometer. The column used was a DB-5 MS, ID 0.18 mm x 10m, 0.18 μm (J&W Scientific) or a VF-5 MS, ID 0.25 mm x 30m, 0.25 μm (Varian Inc.). Typically a linear temperature gradient was applied. The mass spectrometer was equipped with a chemical ionisation (CI) ion source and the reactant gas was methane or 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 3.21 scan/s.

Preparative HPLC was for example performed on a Waters Auto purification HPLC-UV system with a diode array detector using for example a Waters Xterra® MS C_8 column (30x150 mm, 10 µm), a Phenomex Gemini-NX column (21x250 mm, 10 µm), a Waters XBridge C8 column (19x250 mm, 10 µm), or a Waters XBridge™ C18 column (19x250 mm, 10 µm). Mobile phase A: 0.1 M ammonium acetate in water/mobile phase B (95:5). Mobile phase B: MeCN or MeOH. Typically a linear gradient of mobile phase B was applied.

Preparative chiral chromatography for separation of enantiomers was run on a Berger Multigram II system (SFC) or a LaPrep® system (HPLC) using the specified column and mobile phase system.

Terms and abbreviations:

ACN	acetonitrile
aq	aqueous;
Atm	atmospheric pressure;
Boc	*t*-butoxycarbonyl;
Cbz	benzyloxycarbonyl;
dba	dibenzylideneacetone
DCM	dichloromethane;
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine;
DME	1,2-dimethoxyethane
DMF	N,N-dimethyl formamide;
DMSO	dimethyl sulfoxide;
Et_2O	diethyl ether;
EtOAc	ethyl acetate;
equiv.	equivalent
h	hour(s);

HPLC	high performance liquid chromatography;
MeOH	methanol;
min	minute(s);
MS	mass spectrometry
MW	microwave(s)
NMR	nuclear magnetic resonance;
Psi	pounds per square inch;
sat	saturated;
SFC	supercritical fluid chromatography;
TFA	trifluoroacetic acid;
THF	tetrahydrofuran;
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
UPLC	ultra performance liquid chromatography

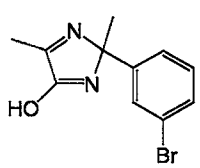
Compounds have been named using CambridgeSoft MedChem ELN v2.1 or ACD/Name, version 10.0, or 10.06, software from Advanced Chemistry Development, Inc. (ACD/Labs), Toronto ON, Canada, www.acdlabs.com, or Lexichem, version 1.7, software from OpenEye.

EXAMPLES

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

Example 1i

2-(3-Bromophenyl)-2,5-dimethyl-2H-imidazol-4-ol

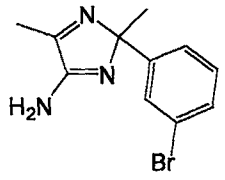


1-(3-Bromophenyl)ethanone (239 µL, 1.80 mmol) was dissolved in ammonia (7M in MeOH) (5.14 mL, 36 mmol). Ethyl 2-oxopropanoate (1 mL, 9 mmol) was added 1 equiv. at a time and the reaction was stirred at 150 °C for 1 h by microwave heating between each addition giving at total of 5 h. The solvent was evaporated and preparative HPLC yielded

76 mg (16% yield) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.62 (br. s., 1 H) 7.65 (t, 1 H) 7.39 - 7.47 (m, 2 H) 7.24 (t, 1 H) 2.27 (s, 3 H) 1.80 (s, 3 H); MS (ES-) *m/z* 265, 267 $[M-H]^-$.

Example 2i

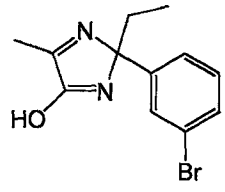
2-(3-Bromophenyl)-2,5-dimethyl-2H-imidazol-4-amine



2-(3-Bromophenyl)-2,5-dimethyl-2H-imidazol-4-ol (76 mg, 0.28 mmol) was dissolved in pyridine (1.5 mL) and phosphorus pentasulfide (76 mg, 0.17 mmol) was added. The reaction was heated to 120 °C for 1 h. Ammonia (7M in MeOH) (4 mL, 28 mmol) and tert-butyl hydroperoxide (0.586 mL, 4.27 mmol) were added and the reaction was stirred at room temperature for 16 h. The solvents were evaporated and preparative HPLC yielded 41 mg (55% yield) of the title compound: MS (ES+) *m/z* 266, 268 $[M+H]^+$.

Example 3i

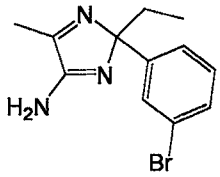
2-(3-Bromophenyl)-2-ethyl-5-methyl-2H-imidazol-4-ol



1-(3-Bromophenyl)propan-1-one (320 mg, 1.50 mmol) was dissolved in ammonia (7M in MeOH) (4 mL, 28 mmol). Ethyl 2-oxopropanoate (1 mL, 9 mmol) was added and the reaction was stirred at 150 °C for 3 h by microwave heating. The solvent was evaporated and preparative HPLC yielded 17 mg (4% yield) of the title compound: MS (ES-) *m/z* 279, 281 $[M-H]^-$.

Example 4i

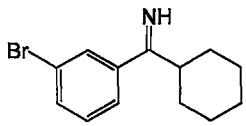
2-(3-Bromophenyl)-2-ethyl-5-methyl-2H-imidazol-4-amine



2-(3-Bromophenyl)-2-ethyl-5-methyl-2H-imidazol-4-ol (16.7 mg, 0.06 mmol) was dissolved in pyridine (1 mL) and phosphorus pentasulfide (50 mg, 0.11 mmol) was added. The reaction was heated to 120 °C for 1 h. Ammonia (33% in water) (0.25 mL, 4.26 mmol) and tert-butyl hydroperoxide (0.122 mL, 0.89 mmol) were added and the reaction was stirred at room temperature for 16 h. The solvent was evaporated and preparative HPLC yielded 9 mg (53% yield) of the title compound: MS (ES+) *m/z* 280, 282 $[M+H]^+$.

Example 5i

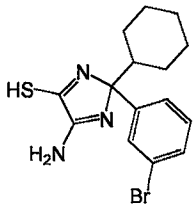
(3-Bromophenyl)(cyclohexyl)methanimine



1,3-Dibromobenzene (3.04 mL, 25.2 mmol) was dissolved in Et_2O (60 mL) and cooled to -78 °C. *n*-Butyllithium (10.1 mL, 25.25 mmol) was added and the the solution stirred for 30 min. Cyclohexanecarbonitrile (2.99 mL, 25.20 mmol) was added in Et_2O (40 mL) at -78 °C and the reaction was allowed to warm to room temperature over 30 min. MeOH (20 mL) containing ammonium acetate (2 g, 25.95 mmol) was added. The solvents were evaporated and the residue taken up in DCM and water. The organic layer was separated and the aqueous phase extracted with DCM. The combined organic phases were shaken with brine and dried over $MgSO_4$. The mixture was filtered and the solvent evaporated to yield 5.56 g (83% yield) of the title compound: MS (ES+) *m/z* 266, 268 $[M+H]^+$.

Example 6i

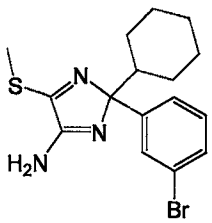
5-Amino-2-(3-bromophenyl)-2-cyclohexyl-2H-imidazole-4-thiol



(3-Bromophenyl)(cyclohexyl)methanimine (5.56 g, 7.73 mmol) and ethanebis(thioamide) (1.47 g, 12.23 mmol) were taken up in EtOH (10 mL). The reaction was heated to 165 °C for 2 h by microwave heating. The solvent was evaporated. Column chromatography using 0% to 100% EtOAc in heptane yielded 1.25 g (46% yield) of the title compound: MS (ES+) *m/z* 352, 354 $[M+H]^+$.

Example 7i

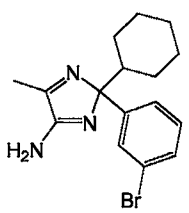
2-(3-Bromophenyl)-2-cyclohexyl-5-(methylthio)-2H-imidazol-4-amine



5-Amino-2-(3-bromophenyl)-2-cyclohexyl-2H-imidazole-4-thiol (1.25 g, 3.55 mmol) was taken up in THF (20 mL). Iodomethane (0.663 mL, 10.64 mmol) was added and the reaction was heated to 60 °C for 24 h. Column chromatography using 0% to 100% EtOAc in heptane yielded 925 mg (71% yield) of the title compound: MS (ES+) m/z 366, 368 $[M+H]^+$.

Example 8i

2-(3-Bromophenyl)-2-cyclohexyl-5-methyl-2H-imidazol-4-amine

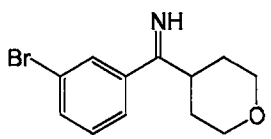


To a solution of zinc iodide (5.0 g, 15.66 mmol) in THF (40 mL) at 0 °C was added methylmagnesium bromide (3M in diethyl ether) (5.22 mL, 15.66 mmol). To the formed

slurry was then added 2-(3-bromophenyl)-2-cyclohexyl-5-(methylthio)-2H-imidazol-4-amine (925 mg, 2.53 mmol) in THF (20 mL), followed by bis(triphenylphosphine)-palladium(II) chloride (177 mg, 0.25 mmol). The reaction mixture was stirred at 50 °C for 3 h. MeOH was added to quench the reaction. The solvent was evaporated. Water was added resulting in a thick slurry which was washed with DCM. The combined organic phases were dried over $MgSO_4$, filtered and the solvent evaporated. Preparative HPLC yielded 120 mg (14% yield) of the title compound: MS (ES+) m/z 334, 336 $[M+H]^+$.

Example 9i

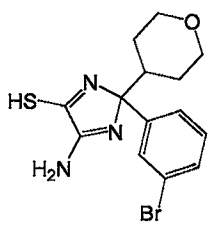
(3-Bromophenyl)(tetrahydro-2H-pyran-4-yl)methanimine



1,3-Dibromobenzene (3.04 mL, 25.2 mmol) was dissolved in Et_2O (60 mL) and cooled to -78 °C. *n*-Butyllithium (10.1 mL, 25.25 mmol) was added and the the solution stirred for 30 min. Tetrahydro-2H-pyran-4-carbonitrile (2.80 g, 25.20 mmol) was added in Et_2O (20 mL) at -78 °C and the reaction was stirred for 30 min. The reaction was then allowed to warm to room temperature over 30 min. MeOH (20 mL) containing ammonium acetate (2 g, 25.95 mmol) was added. The solvents were evaporated and the residue taken up in DCM and water. The organic layer was separated and the aqueous phase extracted with DCM. The combined organic phases were shaken with brine and dried over $MgSO_4$. The mixture was filtered and the solvent evaporated to yield 4.64 g (69% yield) of the title compound: MS (ES+) *m/z* 268, 270 $[M+H]^+$.

Example 10i

5-Amino-2-(3-bromophenyl)-2-(tetrahydro-2H-pyran-4-yl)-2H-imidazole-4-thiol

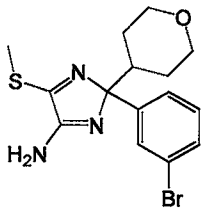


(3-Bromophenyl)(tetrahydro-2H-pyran-4-yl)methanimine (4.64 g, 17.30 mmol) and ethanebis(thioamide) (2.496 g, 20.76 mmol) were taken up in EtOH (10 mL). The reaction

was heated to 165 °C for 2 h by microwave heating. The reaction mixture was diluted with DCM and filtered. Column chromatography using EtOAc 0% to 100% in heptane yielded 3.7 g (60% yield) of the title compound: MS (ES+) *m/z* 354, 356 $[M+H]^+$.

Example 11i

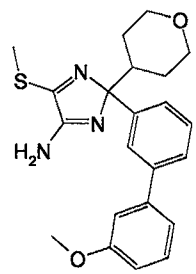
2-(3-Bromophenyl)-5-(methylthio)-2-(tetrahydro-2H-pyran-4-yl)-2H-imidazol-4-amine



5-Amino-2-(3-bromophenyl)-2-(tetrahydro-2H-pyran-4-yl)-2H-imidazole-4-thiol (3.7 g, 10.44 mmol) was taken up in THF (20 mL). Iodomethane (1.951 mL, 31.33 mmol) was added and the reaction was heated to 60 °C for 24 h. Column chromatography using EtOAc 0% to 100% in heptane yielded 2.2 g (57% yield) of the title compound: MS (ES+) *m/z* 368, 370 $[M+H]^+$.

Example 12i

2-(3'-Methoxybiphenyl-3-yl)-5-(methylthio)-2-(tetrahydro-2H-pyran-4-yl)-2H-imidazol-4-amine

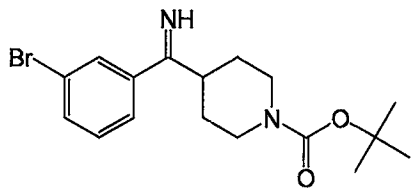


2-(3-Bromophenyl)-5-(methylthio)-2-(tetrahydro-2H-pyran-4-yl)-2H-imidazol-4-amine (625 mg, 1.70 mmol), 3-methoxyphenylboronic acid (258 mg, 1.70 mmol) and bis(triphenylphosphine)palladium(II) chloride (119 mg, 0.17 mmol) were taken up in DME (20 mL) and water (10 mL). Sodium carbonate (1M in water) (4.24 mL, 4.24 mmol) was added and the reaction was heated to 80 °C for 2 h. The reaction mixture was extracted

with DCM. The combined organic phases were dried over $MgSO_4$, filtered and the solvents evaporated. Preparative HPLC yielded 80 mg (12% yield) of the title compound: MS (ES+) *m/z* 396 $[M+H]^+$.

Example 13i

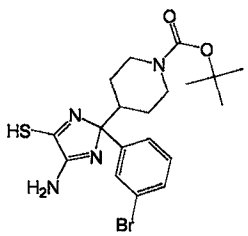
tert-Butyl 4-((3-bromophenyl)(imino)methyl)piperidine-1-carboxylate



1,3-Dibromobenzene (1.435 mL, 11.89 mmol) was dissolved in Et_2O (90 mL) and cooled to -78 °C. n-Butyllithium (5 mL, 12.50 mmol) was added and the solution stirred for 30 min. tert-Butyl 4-cyanopiperidine-1-carboxylate (2.5 g, 11.89 mmol) was added in Et_2O (40 mL) at -78 °C. The reaction was stirred for 30 min and was then allowed to warm to room temperature over 30 min. MeOH (20 mL) containing ammonium acetate (1 g, 13 mmol) was added. The solvents were evaporated and the residue taken up in DCM and water. The organic layer was separated and the aqueous phase extracted with DCM. The combined organic phases were shaken with brine and dried over $MgSO_4$, filtered and the solvent evaporated to yield 2.9 g (66% yield) of the title compound: MS (ES+) *m/z* 367, 369 $[M+H]^+$.

Example 14i

tert-Butyl 4-(4-amino-2-(3-bromophenyl)-5-mercapto-2H-imidazol-2-yl)piperidine-1-carboxylate

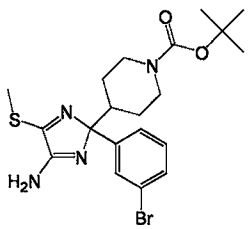


tert-Butyl 4-((3-bromophenyl)(imino)methyl)piperidine-1-carboxylate (2.65 g, 7.22 mmol) and ethanebis(thioamide) (1 g, 8.32 mmol) were taken up in EtOH (10 mL). The reaction was heated to 180 °C for 30 min by microwave heating. The reaction mixture was diluted with DCM and filtered. Column chromatography using EtOAc 0% to 100% in heptane

yielded 943 mg (29% yield) of the title compound: MS (ES+) *m/z* 453, 455 $[M+H]^+$.

Example 15i

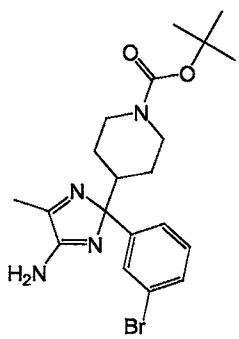
tert-Butyl 4-(4-amino-2-(3-bromophenyl)-5-(methylthio)-2H-imidazol-2-yl)piperidine-1-carboxylate



tert-Butyl 4-(4-amino-2-(3-bromophenyl)-5-mercapto-2H-imidazol-2-yl)piperidine-1-carboxylate (943 mg, 2.08 mmol) was taken up in THF (20 mL). Iodomethane (0.388 mL, 6.24 mmol) was added and the reaction was heated to 60 °C for 24 h. Column chromatography using MeOH, with 0.1% NH_3, 0% to 10% in DCM, yielded 0.57 g (59% yield) of the title compound: MS (ES+) *m/z* 467, 469 $[M+H]^+$.

Example 16i

tert-Butyl 4-(4-amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)piperidine-1-carboxylate

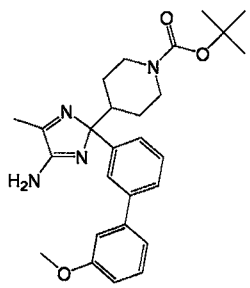


To a solution of zinc iodide (3.41 g, 10.70 mmol) in THF (20 mL) at 0 °C was added methylmagnesium bromide (3M in diethyl ether) (3.57 mL, 10.70 mmol). To the formed slurry was then added bis(triphenylphosphine)palladium(II) chloride (0.150 g, 0.21 mmol) followed by tert-butyl 4-(4-amino-2-(3-bromophenyl)-5-(methylthio)-2H-imidazol-2-yl)piperidine-1-carboxylate (0.5 g, 1.07 mmol) in THF (10 mL). The mixture was stirred at 50 °C for 3 h and then MeOH was added to quench the reaction. Saturated NH_4Cl (aq.) solution was added and the mixture was extracted with diethyl ether. The combined

organic phases were dried over $MgSO_4$, filtered and the solvent evaporated. Preparative HPLC yielded 44.5 mg (9.5% yield) of the title compound: MS (ES+) *m/z* 435, 437 $[M+H]^+$.

Example 17i

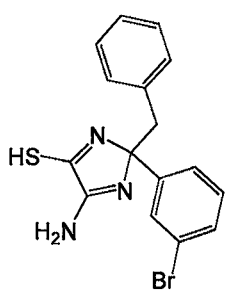
tert-Butyl 4-(4-amino-2-(3'-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)piperidine-1-carboxylate



tert-Butyl 4-(4-amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)piperidine-1-carboxylate (44.5 mg, 0.10 mmol), 3-methoxyphenylboronic acid (18.64 mg, 0.12 mmol) and bis(triphenylphosphine)palladium(II) chloride (7.17 mg, 10.22 μmol) were taken up in DME (1 mL) and water (0.5 mL). Sodium carbonate (1M in water) (0.256 mL, 0.26 mmol) was added and the reaction was heated to 80 °C for 2 h. The reaction mixture was filtered and preparative HPLC yielded 15.7 mg (33% yield) of the title compound: MS (ES+) *m/z* 463 $[M+H]^+$.

Example 18i

5-Amino-2-benzyl-2-(3-bromophenyl)-2H-imidazole-4-thiol

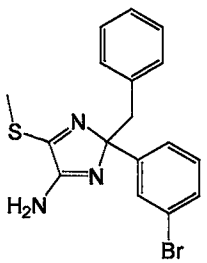


1-(3-bromophenyl)-2-phenylethanone (1 g, 3.63 mmol) and ethanebis(thioamide) (1.311 g, 10.9 mmol) were taken up in ammonia (7M in MeOH) (15 mL, 105 mmol). The reaction was heated to 150 °C for 1 h by microwave heating. The reaction mixture was diluted with DCM and filtered. Column chromatography using EtOAc 0% to 100% in heptane yielded

1.232 g (94% yield) of the title compound: MS (ES+) *m/z* 360, 362 $[M+H]^+$.

Example 19i

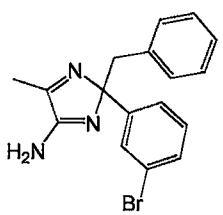
2-Benzyl-2-(3-bromophenyl)-5-(methylthio)-2H-imidazol-4-amine



5-Amino-2-benzyl-2-(3-bromophenyl)-2H-imidazole-4-thiol (1.232 g, 3.42 mmol) was taken up in THF (30 mL). Iodomethane (0.639 mL, 10.26 mmol) was added and the reaction was heated to 60 °C for 4 h. Column chromatography using 0% to 100% EtOAc in heptane yielded 200 mg (16% yield) of the title compound: MS (ES+) *m/z* 374, 376 $[M+H]^+$.

Example 20i

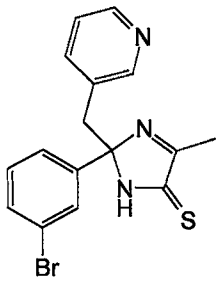
2-Benzyl-2-(3-bromophenyl)-5-methyl-2H-imidazol-4-amine



2-Benzyl-2-(3-bromophenyl)-5-(methylthio)-2H-imidazol-4-amine (200 mg, 0.53 mmol) and 1,3-bis(diphenylphosphino)propane nickel (II) chloride (116 mg, 0.21 mmol) were dissolved in toluene (3 mL). Methylmagnesium bromide (3M in diethyl ether) (1.425 mL, 4.27 mmol) was added and the resulting suspension was stirred at room temperature. After 1 h, water was added and the phases were separated. The aqueous phase was extracted with DCM. The combined organic phases were dried over $MgSO_4$, filtered and the solvents evaporated. Preparative HPLC yielded 66.5 mg (36% yield) of the title compound: MS (ES+) *m/z* 342, 344 $[M+H]^+$.

Example 21i

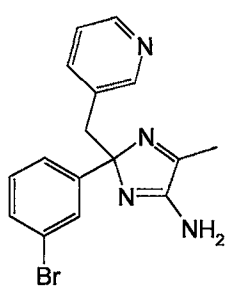
2-(3-Bromophenyl)-4-methyl-2-(pyridin-3-ylmethyl)-1H-imidazole-5(2H)-thione



Lithium diisopropylamide (25.00 mL, 45.00 mmol) was added dropwise over 20 min to solution of 3-picoline (4.39 mL, 45.00 mmol) in THF (50 mL) under a nitrogen atmosphere at -10 °C. The resulting mixture was stirred at -10 °C for 30 min and then a solution of 3-bromobenzonitrile (2.73 g, 15 mmol) in THF (10 mL) was added drowise over 5 min and the resulting mixture was stirred at -10 °C for 15 min. The cooling bath was removed and the mixture was stirred at rt for 2 h. A solution of ammonium acetate (3.23 mL, 45.00 mmol) in MeOH (20 mL) was added, the mixture stirred for 10 min and then the solvents were removed *in vacuo*. The resulting residue was taken up in DCM (50 mL) and water (30 mL) and poured into a phase separator. The organic phase was collected and concentrated. The resulting residue was taken up in MeOH (15 mL), 2-oxopropanethioamide (2.63 g, 25.50 mmol) was added and the mixture was stirred at 50 °C over night. When cooled to rt the mixture was concentrated onto silica and purified on a silica gel column eluted with 0-100% EtOAc in heptane to give 790 mg (15% yield) of the title compound: MS (ES-) *m/z* 358, 360 $[M-1]^-$.

Example 22i

2-(3-Bromophenyl)-5-methyl-2-(pyridin-3-ylmethyl)-2H-imidazol-4-amine

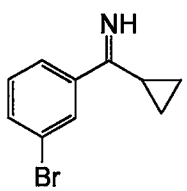


2-(3-Bromophenyl)-4-methyl-2-(pyridin-3-ylmethyl)-1H-imidazole-5(2H)-thione (790 mg, 2.19 mmol) and 7M ammonia in MeOH (9.398 mL, 65.79 mmol) were mixed and heated

in a microwave reactor at 100 °C for 1 h. The mixture was concentrated and the resulting residue was taken up in 1:1 EtOAc/toluene (10 mL) and 1M aqueous citric acid (10 mL). The aqueous phase was separated and the organic phase was extracted with 1M citric acid (10 mL). The combined aqueous phase was extracted with toluene (5 mL) and then made alkaline to pH~8 with 50% aqueous NaOH and extracted with DCM (3 x 5 mL). The combined organic phase was passed through a phase separator, concentrated and purified on a silica gel column eluted with 0-15% 0.1M NH_3 in MeOH in DCM to give 205 mg (27% yield) of the title compound: MS (ES-) *m/z* 341, 343 $[M-1]^-$.

Example 23i

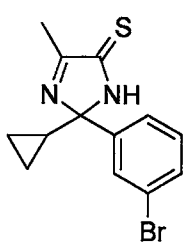
(3-Bromophenyl)(cyclopropyl)methanimine



3-Bromobenzonitrile (1.1 g, 6.04 mmol) was dissolved in THF (3 mL) and cyclopropylmagnesium bromide (0.5 M in THF, 13.30 mL, 6.65 mmol) was added dropwise. Copper(I) bromide (0.017 g, 0.12 mmol) was added immediately after. The mixture was heated to 40 °C for 18 h, cooled to rt and then ammonium acetate (0.699 g, 9.07 mmol) in methanol (5 mL) was added. The mixture was concentrated. DCM and water was added and the organic phase was collected, dried over $MgSO_4$ and concentrated to give 1.3 g (96% yield). The compound was used directly in the next step: MS (CI) *m/z* 224, 226 $[M+1]^+$.

Example 24i

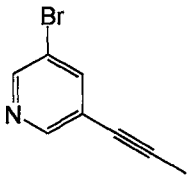
2-(3-Bromophenyl)-2-cyclopropyl-4-methyl-1H-imidazole-5(2H)-thione



(3-Bromophenyl)(cyclopropyl)methanimine (1.900 g, 8.48 mmol) was dissolved in dry methanol (20 mL) under argon and 2-oxopropanethioamide (1.312 g, 12.72 mmol) was added in one portion. The solution was heated at 50 °C for 3.5 h. The reaction was allowed to cool to rt and the solvents were evaporated at reduced pressure. Chromatography using 0–30% EtOAc in n-heptane gave 2 g (76% yield) of the title compound: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.57 (s, 1 H) 7.68 (t, 1 H) 7.54 - 7.61 (m, 1 H) 7.49 - 7.54 (m, 1 H) 7.37 (t, 1 H) 2.23 (s, 3 H) 1.60 (tt, 1 H) 0.43 - 0.57 (m, 2 H) 0.33 - 0.43 (m, 1 H) 0.15 - 0.27 (m, 1 H). MS (ES) *m/z* 309, 311 $[M+1]^+$.

Example 25i

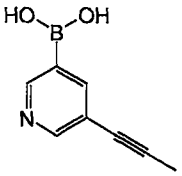
3-Bromo-5-(prop-1-ynyl)pyridine



To a solution of 3,5-dibromopyridine (5 g, 21.11 mmol), copper(I) iodide (0.238 mL, 6.33 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.220 g, 1.06 mmol) in toluene (250 mL) was added 1-(trimethylsilyl)-1-propyne (3.16 mL, 21.11 mmol), triethylamine (9.71 mL, 69.65 mmol) and 1M tetrabutylammonium fluoride in THF (21.11 mL, 21.11 mmol) and the resulting mixture was stirred under a nitrogen atmosphere at rt over night. The mixture was concentrated and the resulting residue was taken up in water (20 mL) and DCM (20mL) and poured into a phase separator. The organic phase was collected and the aqueous phase was extracted once with DCM (20 mL). The combined organics were concentrated and purified on a silica gel column eluted with 0-30% EtOAc in heptane to give 2.93 g (71% yield) of the title compound: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.66 (d, 1 H) 8.58 (d, 1 H) 8.12 (t, 1 H) 2.10 (s, 3 H); MS (CI) *m/z* 196, 198 $[M+H]^+$.

Example 26i

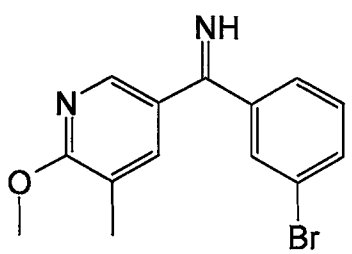
5-(Prop-1-ynyl)pyridin-3-yl boronic acid



n-Butyllithium (7.17 mL, 17.93 mmol) was added dropwise over 10 min to a solution of 3-bromo-5-(prop-1-ynyl)pyridine (2.93 g, 14.95 mmol) and triisopropyl borate (4.14 mL, 17.93 mmol) in THF (6 mL) and toluene (24 mL) at -78 °C under a nitrogen atmosphere. The resulting mixture was stirred at -78 °C for 45 min. The cooling bath was removed and the mixture was stirred at rt for 30 min before being cooled to -10 °C. Aqueous 2M HCl (15 mL) was added, the cooling bath removed and the mixture was stirred at rt for 1 h. The organics were removed under reduced pressure and the pH of the resulting aqueous residue was adjusted to 7-8 using an aqueous 20% NaOH solution. The aqueous mixture was diluted with brine (20 mL) and then saturated with solid NaCl and extracted with THF (3 x 25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. Recrystallization from MeOH gave 1.5 g (62% yield) of the title compound: MS (ES-) *m/z* 160 $[M-1]^-$.

Example 27i

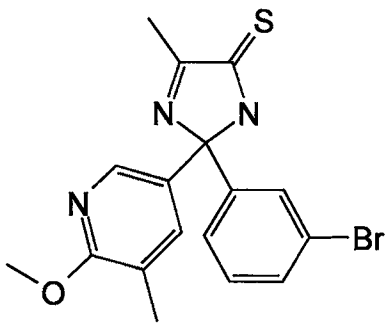
(3-Bromophenyl)(6-methoxy-5-methylpyridin-3-yl)methanimine



n-Butyllithium was added drop wise to a solution of 5-bromo-2-methoxy-3-methylpyridine (0.502 g, 2.48 mmol) in dry Et_2O (10 mL) cooled at -78 °C under an atmosphere of argon. The mixture was stirred at -78 °C for 20 minutes and then a solution of 3-bromobenzonitrile (0.452 g, 2.48 mmol) in dry Et_2O (2.0 mL) was added dropwise. The reaction was stirred for 30 minutes at -78 °C and then dry MeOH (2 mL) was added dropwise to quench the reaction. The solvents were evaporated under reduced pressure at a heating bath temperature of 20 °C. The residue was dissolved in DCM, washed once with cold water, passed through a phase separator and the solvents were removed at reduced pressure to give the title compound that was used without purification directly in the next reaction: MS (CI+) m/z 305, 307 $[M+H]^+$.

Example 28i

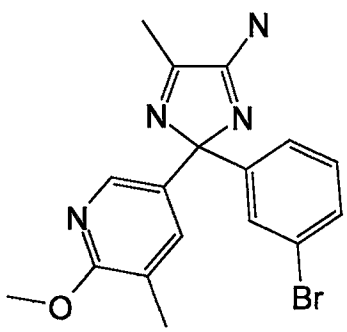
2-(3-Bromophenyl)-2-(6-methoxy-5-methylpyridin-3-yl)-4-methyl-1H-imidazole-5(2H)-thione



To a solution of crude (3-bromophenyl)(6-methoxy-5-methylpyridin-3-yl)methanimine (0.750 g, 2.46 mmol) in dry MeOH (10 mL) under argon was added 2-oxopropanethioamide (0.406 g, 3.93 mmol) in one portion. The mixture was stirred at rt for 60 minutes and then the reaction was heated at 50 °C for 17 hours and then 13 hours at 60 °C to achieve full conversion. The reaction was allowed to cool to rt and the solvents were evaporated to give the title compound that was used without purification in the next reaction: MS (ES+) m/z 390, 392 $(M+H)^+$.

Example 29i

2-(3-Bromophenyl)-2-(6-methoxy-5-methylpyridin-3-yl)-5-methyl-2H-imidazol-4-amine

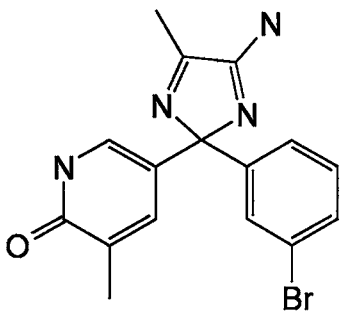


2-(3-Bromophenyl)-2-(6-methoxy-5-methylpyridin-3-yl)-4-methyl-1H-imidazole-5(2H)-thione (0.950 g, 2.43 mmol) was dissolved in ammonia (7M in MeOH, 12.17 mL, 85.19 mmol) and heated with microwaves in a sealed vial at 100 °C for 1 h. The solvents were evaporated *in vacuo*, another portion of ammonia (7M in MeOH, 12.17 mL, 85.19 mmol) was added and the reaction was heated with microwaves in a sealed vial at 100 °C for 1 h. The solvent was evaporated *in vacuo* and the residue was partiotioned between EtOAc (50

mL) and aqueous 1M HCl (15 mL). The layers were separated and the organics extracted with aqueous 1M HCl (2 x 15 mL). The aqueous phases were combined, EtOAc (~20 mL) was added, and the mixture was made basic with saturated aqueous $NaHCO_3$. The product was extracted with dichloromethane (2 x 100 mL), dried (Na_2SO_4), filtered and evaporated to give 2-(3-bromophenyl)-2-(6-methoxy-5-methylpyridin-3-yl)-5-methyl-2H-imidazol-4-amine (0.440 g, 48% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (d, 1 H) 7.62 (t, 1 H) 7.59 (d, 1 H) 7.51 (d, 1 H) 7.39 (m, 1 H) 7.24 (m, 1 H) 6.73 (br. s., 2 H) 3.81 (s, 3 H) 2.24 (s, 3 H) 2.08 (s, 3 H); MS (ES+) m/z 373, 375 $[M+H]^+$.

Example 30i

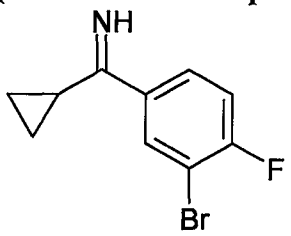
5-(4-Amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-3-methylpyridin-2(1H)-one



Aqueous 3M HCl (7.95 mL, 23.86 mmol) was added to a stirred solution of 2-(3-bromophenyl)-2-(6-methoxy-5-methylpyridin-3-yl)-5-methyl-2H-imidazol-4-amine (424 mg, 1.14 mmol) in tetrahydrofuran (8 mL) in a microwave vial. The vial was sealed and heated with microwaves at 100 °C for 45 minutes. The tetrahydrofuran was removed by evaporation, and the remaining aqueous phase basified with saturated aqueous $NaHCO_3$ and then extracted with EtOAc. The organics were combined, dried (Na_2SO_4), filtered and evaporated to give 540 mg of the title compound that was used as such in the next step: MS (ES+) m/z 359, 361 $[M+H]^+$.

Example 31i

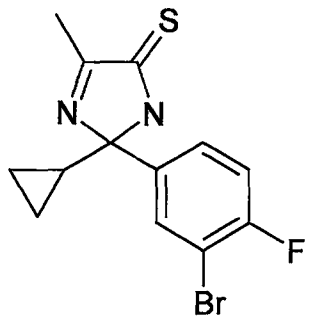
(3-Bromo-4-fluorophenyl)(cyclopropyl)methanimine



3-Bromo-4-fluorobenzonitrile (1.0 g, 5.00 mmol) was dissolved in THF (3 mL) and cyclopropylmagnesium bromide (0.5 M in THF, 11.00 mL, 5.50 mmol) was added dropwise, directly followed by addition of copper(I) bromide (0.014 g, 0.10 mmol). The mixture was heated to 40 °C for 19 h, cooled to rt and then ammonium acetate (0.578 g, 7.50 mmol) in methanol (5 mL) was added. The mixture was concentrated and then partitioned between DCM and water. The organic phase was collected, dried over Na_2SO_4 and concentrated to give 1.20 g (99% yield) of the title compound that was used directly in next step: MS (EI) m/z 240, 242 $[M]^+$.

Example 32i

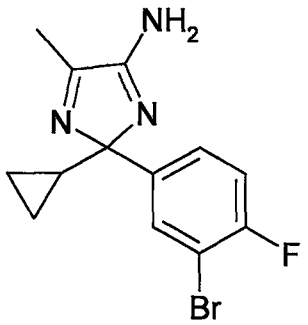
2-(3-Bromo-4-fluorophenyl)-2-cyclopropyl-4-methyl-1H-imidazole-5(2H)-thione



(3-Bromo-4-fluorophenyl)(cyclopropyl)methanimine (1.200 g, 4.96 mmol) was dissolved in dry methanol (7 mL) under argon, and 2-oxopropanethioamide (0.869 g, 8.43 mmol) was added in one portion. The solution was heated at 50 °C for 17 h. The reaction was allowed to cool to rt and the solvents were evaporated at reduced pressure. Silica chromatography using 0–100% EtOAc in n-heptane gave 0.506 g (31% yield) of the title compound: MS (ES) m/z 327, 329 $[M+1]^+$.

Example 33i

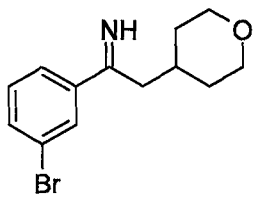
2-(3-Bromo-4-fluorophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine



2-(3-Bromo-4-fluorophenyl)-2-cyclopropyl-4-methyl-1H-imidazole-5(2H)-thione (0.506 g, 1.55 mmol) and 7N ammonia in MeOH (15.46 mL, 108.25 mmol) were heated to 45 °C overnight. The mixture was concentrated and another portion of 7N ammonia in MeOH (15.46 mL, 108.25 mmol) was added, followed by heating as above. This cycle was repeated twice more. The reaction mixture was concentrated and purified by column chromatography with a gradient of 0-100% EtOAc in heptane to give 250 mg (52% yield) of the title compound: 1H NMR (500 MHz, DMSO-d_6) δ ppm 7.76 (dd, 1 H) 7.51 - 7.67 (m, 1 H) 7.29 (t, 1 H) 6.57 (br. s., 2 H) 2.15 (s, 3 H) 1.42 - 1.51 (m, 1 H) 0.24 - 0.36 (m, 2 H) 0.15 - 0.26 (m, 1 H), -0.10 - 0.06 (m, 1 H); MS (ES+) m/z 310, 312 $[M+H]^+$.

Example 34i

1-(3-Bromophenyl)-2-(tetrahydro-2H-pyran-4-yl)ethanimine

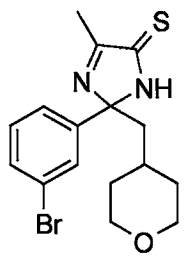


Magnesium (0.668 g, 27.47 mmol) and 2 small crystals of I_2 was stirred under Ar(g) for 5 min. THF (5 mL) was added followed by dropwise addition of 4-(bromomethyl)tetrahydro-2H-pyran (2.95 g, 16.48 mmol) in THF (10 mL). The mixture was heated at 45 °C for 1.5 h and then transferred to a flask containing 3-bromobenzonitrile (2 g, 10.99 mmol) and copper(I) bromide (0.032 g, 0.22 mmol) in THF (4 mL). The mixture was heated to 45 °C for 2 h. Ammonium acetate (1.270 g, 16.48 mmol) in methanol (7 mL) was added and after

10 min DCM and water was added. The organic phase was dried over $MgSO_4$ and concentrated to give 3.05 g (98% yield) ot the title compound that was used directly in the next step: MS(CI) *m/z* 282, 284 $[M+1]^+$.

Example 35i

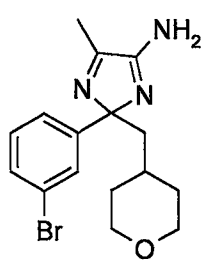
2-(3-Bromophenyl)-4-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazole-5(2H)-thione



The title compound was synthesized as described for Example 24i in 76% yield starting from 1-(3-bromophenyl)-2-(tetrahydro-2H-pyran-4-yl)ethanimine (3.05 g, 10.81 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.73 (s, 1 H) 7.68 (s, 1 H) 7.50 - 7.57 (m, 2 H) 7.37 (t, 1 H) 3.71 (t, 2 H) 3.09 - 3.18 (m, 2 H) 2.25 (s, 3 H) 2.04 - 2.10 (m, 1 H) 1.85 - 1.91 (m, 1 H) 1.45 (d, 1 H) 1.33 (d, 1 H) 1.20 - 1.30 (m, 1 H) 1.09 - 1.19 (m, 2 H). MS (ES) *m/z* 367, 369 $[M+1]^+$.

Example 36i

2-(3-Bromophenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine

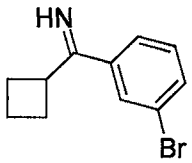


The title compound was synthesized as described for Example 13 in 35% yield starting from 2-(3-bromophenyl)-4-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazole-5(2H)-thione (3.01 g, 8.19 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.66 (t, 1 H) 7.53 - 7.58 (m, 1 H) 7.38 - 7.43 (m, 1 H) 7.25 (t, 1 H) 6.48 (s, 2 H) 3.64 - 3.72 (m, 2 H)

3.06 - 3.15 (m, 2 H) 2.15 (s, 3 H) 1.83 (dd, 1 H) 1.60 (dd, 1 H) 1.43 - 1.50 (m, 1 H) 1.34 - 1.41 (m, 1 H) 1.20 - 1.30 (m, 1 H) 0.98 - 1.11 (m, 2 H); MS (ES) *m/z* 350, 352 $[M+1]^+$.

Example 37i

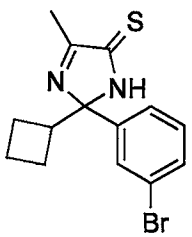
(3-Bromophenyl)(cyclobutyl)methanimine



The title compound was synthesized as described for Example 34i in 97% yield starting from bromocyclobutane (1.061 g, 7.86 mmol) and 3-bromobenzonitrile (1.1 g, 6.04 mmol): MS (CI) *m/z* 238, 240 $[M+1]^+$.

Example 38i

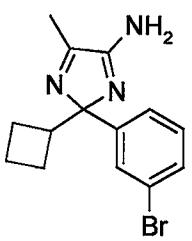
2-(3-Bromophenyl)-2-cyclobutyl-4-methyl-1H-imidazole-5(2H)-thione



The title compound was synthesized as described for Example 24i in 65% yield starting from (3-bromophenyl)(cyclobutyl)methanimine (1.4 g, 5.88 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.77 (br. s., 1 H) 7.66 (t, 1 H) 7.53 - 7.56 (m, 1 H) 7.49 - 7.52 (m, 1 H) 7.34 - 7.39 (m, 1 H) 3.05 - 3.13 (m, 1 H) 2.27 (s, 3 H) 1.66 - 1.78 (m, 4 H) 1.53 - 1.66 (m, 2 H); MS (ES) *m/z* 323, 325 $[M+1]^+$.

Example 39i

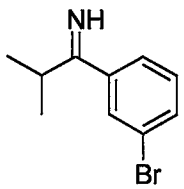
2-(3-Bromophenyl)-2-cyclobutyl-5-methyl-2H-imidazol-4-amine



The title compound was synthesized as described for Example 13 in 38% yield starting from 2-(3-bromophenyl)-2-cyclobutyl-4-methyl-1H-imidazole-5(2H)-thione (1.24 g, 3.84 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.67 (t, 1 H) 7.53 - 7.58 (m, 1 H) 7.37 - 7.42 (m, 1 H) 7.24 (t, 1 H) 6.53 (s, 2 H) 2.88 - 2.97 (m, 1 H) 2.18 (s, 3 H) 1.47 - 1.70 (m, 6 H); MS (ES) *m/z* 306, 308 $[M+1]^+$.

Example 40i

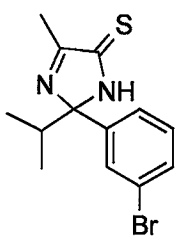
1-(3-Bromophenyl)-2-methylpropan-1-imine



The title compound was synthesized as described for Example 23i in 90% yield starting from isopropylmagnesium bromide (15.28 mL, 15.28 mmol) and 3-bromobenzonitrile (2.14 g, 11.76 mmol): MS (CI) *m/z* 226, 228 $[M+1]^+$.

Example 41i

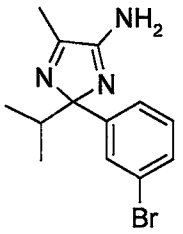
2-(3-Bromophenyl)-2-isopropyl-4-methyl-1H-imidazole-5(2H)-thione



The title compound was synthesized as described for Example 24i in 52% yield starting from 1-(3-bromophenyl)-2-methylpropan-1-imine (2.4 g, 10.61 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.72 (br. s., 1 H) 7.67 (t, 1 H) 7.53 - 7.57 (m, 1 H) 7.50 - 7.53 (m, 1 H) 7.35 - 7.39 (m, 1 H) 2.33 - 2.41 (m, 1 H) 2.25 (s, 3 H) 0.69 - 0.76 (m, 6 H); MS (ES) *m/z* 311, 313 $[M+1]^+$.

Example 42i

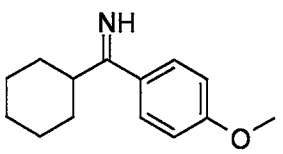
2-(3-Bromophenyl)-2-isopropyl-5-methyl-2H-imidazol-4-amine



The title compound was synthesized as described for Example 13 in 41% yield starting from 2-(3-bromophenyl)-2-isopropyl-4-methyl-1H-imidazole-5(2H)-thione (1.7 g, 5.46 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δppm 7.66 (t, 1 H) 7.52 - 7.57 (m, 1 H) 7.38 - 7.43 (m, 1 H) 7.25 (t, 1 H) 6.49 (br. s., 2 H) 2.16 (s, 3 H) 2.09 - 2.15 (m, 1 H) 0.72 (d, 3 H) 0.61 (d, 3 H); MS (ES) *m/z* 294, 296 $[M+1]^+$.

Example 43i

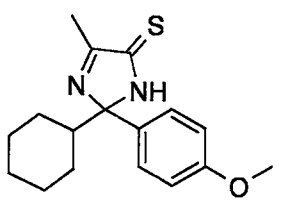
Cyclohexyl(4-methoxyphenyl)methanimine



The title compound was synthesized as described for Example 34i in 97% yield starting from bromocyclohexane (0.796 g, 4.88 mmol) and 4-methoxybenzonitrile (0.5 g, 3.76 mmol): MS (CI) *m/z* 218 $[M+1]^+$.

Example 44i

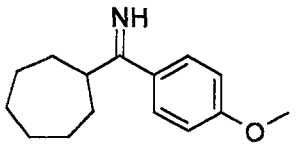
2-Cyclohexyl-2-(4-methoxyphenyl)-4-methyl-1H-imidazole-5(2H)-thione



The title compound was synthesized as described for Example 24i in 49% yield starting from cyclohexyl(4-methoxyphenyl)methanimine (0.8 g, 3.68 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.65 (s, 1 H) 7.32 - 7.40 (m, 2 H) 6.87 - 6.95 (m, 2 H) 3.72 (s, 3 H) 2.21 (s, 3 H) 1.88 - 1.95 (m, 1 H) 1.57 - 1.67 (m, 2 H) 1.50 - 1.57 (m, 1 H) 1.33 - 1.42 (m, 2 H) 1.01 - 1.14 (m, 2 H) 0.90 - 1.01 (m, 1 H) 0.77 - 0.89 (m, 2 H); MS (ES) *m/z* 303 $[M+1]^+$.

Example 45i

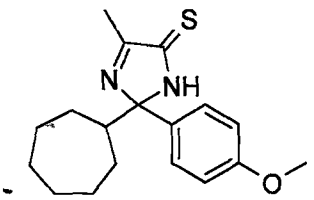
Cycloheptyl(4-methoxyphenyl)methanimine



The title compound was synthesized as described for Example 34i in 90% yield starting from bromocycloheptane (0.864 g, 4.88 mmol) and 4-methoxybenzonitrile (0.5 g, 3.76 mmol): MS (CI) *m/z* 232 $[M+1]^+$.

Example 46i

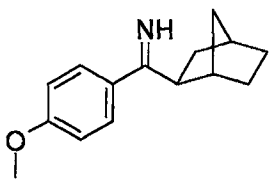
2-Cycloheptyl-2-(4-methoxyphenyl)-4-methyl-1H-imidazole-5(2H)-thione



The title compound was synthesized as described for Example 24i in 39% yield starting from cycloheptyl(4-methoxyphenyl)methanimine (0.78 g, 3.37 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.62 (br. s., 1 H) 7.33 - 7.40 (m, 2 H) 6.89 - 6.95 (m, 2 H) 3.74 (s, 3 H) 2.23 (s, 3 H) 2.17 - 2.22 (m, 1 H) 1.34 - 1.57 (m, 8 H) 1.26 - 1.31 (m, 2 H) 0.96 - 1.12 (m, 2 H); MS (ES) *m/z* 317 $[M+1]^+$.

Example 47i

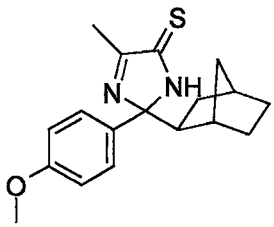
Bicyclo[2.2.1]heptan-2-yl(4-methoxyphenyl)methanimine



The title compound was synthesized as described for Example 34i in 90% yield starting from (1R,2R,4S)-2-bromobicyclo[2.2.1]heptane (0.657 g, 3.76 mmol) and 4-methoxybenzonitrile (0.5 g, 3.76 mmol): MS (EI) *m/z* 229 $[M]^+$.

Example 48i

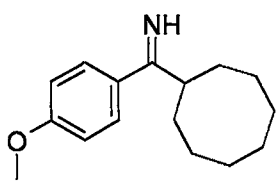
2-(Bicyclo[2.2.1]heptan-2-yl)-2-(4-methoxyphenyl)-4-methyl-1H-imidazole-5(2H)-thione



The title compound was synthesized as described for Example 24i in 10% yield starting from (1S,2S,4R)-bicyclo[2.2.1]heptan-2-yl(4-methoxyphenyl)methanimine (0.9 g, 3.92 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.62 (br. s., 1 H) 7.39 - 7.45 (m, 2 H) 6.89 - 6.95 (m, 2 H) 3.73 - 3.75 (m, 3 H) 2.23 - 2.27 (m, 3 H) 2.15 - 2.22 (m, 1 H) 2.10 - 2.14 (m, 1 H) 1.77 - 1.85 (m, 1 H) 1.30 - 1.46 (m, 2 H) 1.21 - 1.30 (m, 2 H) 1.14 - 1.21 (m, 1 H) 1.00 - 1.10 (m, 2 H) 0.90 - 0.98 (m, 1 H); MS (ES) *m/z* 315 $[M+1]^+$.

Example 49i

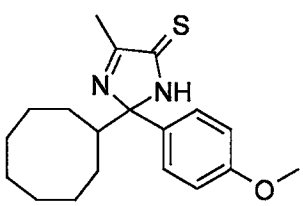
Cyclooctyl(4-methoxyphenyl)methanimine



The title compound was synthesized as described for Example 34i in 85% yield starting from bromocyclooctane (0.933 g, 4.88 mmol) and was used directly in the next step.

Example 50i

2-Cyclooctyl-2-(4-methoxyphenyl)-4-methyl-1H-imidazole-5(2H)-thione

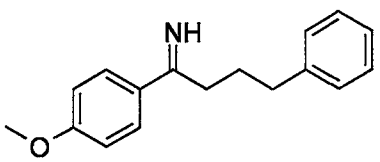


The title compound was synthesized as described for Example 24i in 4% yield starting from cyclooctyl(4-methoxyphenyl)methanimine (0.9 g, 3.67 mmol): ^{1}H NMR (500 MHz,

DMSO-d_6) δ ppm 12.44 (br. s., 1 H) 7.21 - 7.26 (m, 2 H) 6.77 - 6.81 (m, 2 H) 3.60 (s, 3 H) 2.16 - 2.21 (m, 1 H) 2.09 (s, 3 H) 1.21 - 1.45 (m, 10 H) 1.03 - 1.19 (m, 4 H); MS (ES) *m/z* 331 $[M+1]^+$.

Example 51i

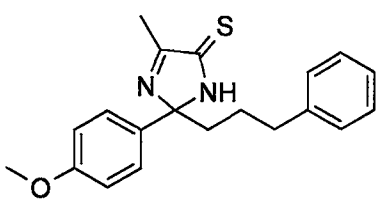
1-(4-Methoxyphenyl)-4-phenylbutan-1-imine



The title compound was synthesized as described for Example 34i in 100% yield starting from (3-bromopropyl)benzene (1 g, 5,02 mmol) and 4-methoxybenzonitrile (0,669 g, 5,02 mmol): MS (CI) *m/z* 254 $[M+1]^+$.

Example 52i

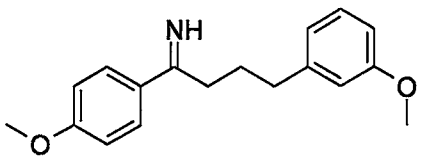
2-(4-Methoxyphenyl)-4-methyl-2-(3-phenylpropyl)-1H-imidazole-5(2H)-thione



The title compound was synthesized as described for Example 24i in 63% yield starting from 1-(4-methoxyphenyl)-4-phenylbutan-1-imine (0.5 g, 1.97 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.14 (br. s., 1 H) 7.24 - 7.29 (m, 4 H) 7.16 - 7.22 (m, 1 H) 7.08 - 7.13 (m, 2 H) 6.84 - 6.91 (m, 2 H) 3.80 (s, 3 H) 2.54 - 2.65 (m, 2 H) 2.38 (s, 3 H) 2.13 - 2.18 (m, 2 H) 1.43 - 1.60 (m, 2 H); MS (ES) *m/z* 339 $[M+1]^+$.

Example 53i

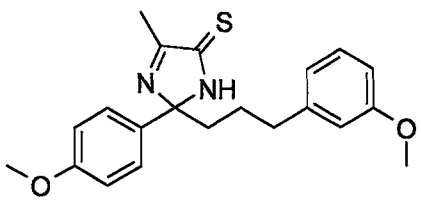
4-(3-Methoxyphenyl)-1-(4-methoxyphenyl)butan-1-imine



The title compound was synthesized as described for Example 34i in 100% yield starting from 1-(3-bromopropyl)-3-methoxybenzene (0.516 g, 2.25 mmol) and 4-methoxybenzonitrile (0.3 g, 2.25 mmol): MS (CI) *m/z* 284 $[M+1]^+$.

Example 54i

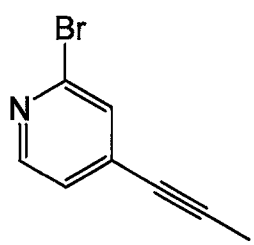
2-(4-Methoxyphenyl)-2-(3-(3-methoxyphenyl)propyl)-4-methyl-1H-imidazole-5(2H)-thione



The title compound was synthesized as described for Example 24i in 32% yield starting from 4-(3-methoxyphenyl)-1-(4-methoxyphenyl)butan-1-imine (0.64 g, 2.26 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.69 (s, 1 H) 7.32 - 7.38 (m, 2 H) 7.16 (t, 1 H) 6.89 - 6.94 (m, 2 H) 6.70 - 6.74 (m, 1 H) 6.64 - 6.70 (m, 2 H) 3.73 (s, 3 H) 3.70 (s, 3 H) 2.45 - 2.49 (m, 2 H) 2.22 (s, 3 H) 1.93 - 2.01 (m, 2 H) 1.28 - 1.36 (m, 2 H); MS (ES) *m/z* 369 $[M+1]^+$.

Example 55i

2-Bromo-4-(prop-1-ynyl)pyridine

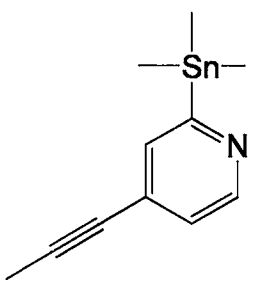


To a solution of 2-bromo-4-iodopyridine (2 g, 7.04 mmol), copper(I) iodide (0.080 mL, 2.11 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.407 g, 0.35 mmol) in toluene (85 mL) was added 1-(trimethylsilyl)-1-propyne (1.054 mL, 7.04 mmol), triethylamine (3.24 mL, 23.25 mmol) and tetrabutylammonium fluoride (1 M in THF, 7.04 mL, 7.04

mmol) and the resulting mixture was stirred under an argon atmosphere at room temperature over night. The mixture was concentrated and the resulting residue was partitioned between water (10 mL) and dichloromethane (10 mL) and poured into a phase separator. The organic phase was collected and the aqueous phase was extracted once with dichloromethane (10 mL). The combined organics were concentrated and purified by silica gel chromatography using 0% to 30% ethyl acetate in heptane to give 2-bromo-4-(prop-1-ynyl)pyridine (1.195 g, 87% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.35 (dd, 1 H) 7.65 (s, 1 H) 7.42 (dd, 1 H) 2.11 (s, 3 H); MS (ES+) *m/z* 196, 198 $[M+H]^+$; MS (APCI+) *m/z* 196, 198 $[M+H]^+$

Example 56i

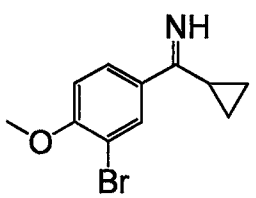
4-(Prop-1-ynyl)-2-(trimethylstannyl)pyridine



2-Bromo-4-(prop-1-ynyl)pyridine (1.077 g, 5.49 mmol) was dissolved in toluene (30 mL) and 1,1,1,2,2,2-hexamethyldistannane (2.278 mL, 10.99 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.635 g, 0.55 mmol) were added and the reaction was stirred at 80 °C over night under argon atmosphere. The mixture was cooled to room temperature and filtered through a pad of Celite and concentrated *in vacuo*. Toluene (20 mL) was added and the mixture was concentrated *in vacuo to yield the title comound that was* used as such in the next step: MS (APCI+) *m/z* 282 $(M+H)^+$.

Example 57i

(3-Bromo-4-methoxyphenyl)(cyclopropyl)methanimine

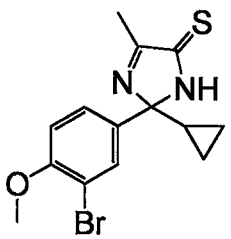


3-Bromo-4-methoxybenzonitrile (2.00 g, 9.43 mmol) and copper(I) bromide (0.068 g, 0.47

mmol) were dissolved in THF (15.0 mL) under argon and then heated to 40 °C. Cyclopropylmagnesium bromide (0.5 M in THF) (20.75 mL, 10.38 mmol) was added. The resulting mixture was stirred at 40 °C for 3 h, then additional cyclopropylmagnesium bromide (0.5 M in THF) (9.43 mL, 4.72 mmol) was added and the resulting mixture was stirred at 40 °C for 2 h. The reaction was quenched by addition of ammonium acetate (1.091 g, 14.15 mmol) in methanol (30.0 mL). The mixture was partitioned between water and dichloromethane (twice). The organic layers were collected and concentrated *in vacuo* to give crude (3-bromo-4-methoxyphenyl)(cyclopropyl)methanimine (2.57 g,quantitative yield) That was used as such in the next step: MS (APCI+) *m/z* 254, 256 $[M+H]^+$.

Example 58i

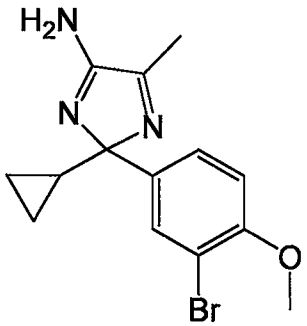
2-(3-Bromo-4-methoxyphenyl)-2-cyclopropyl-4-methyl-1H-imidazole-5(2H)-thione



(3-Bromo-4-methoxyphenyl)(cyclopropyl)methanimine (2.57 g, 10.11 mmol) and 2-oxopropanethioamide (1.773 g, 17.19 mmol) were stirred in MeOH (10 mL) at 50 °C for 4 h, then the mixture was concentrated *in vacuo*. Purification was achieved by silica chromatography using 0% to 20% ethyl acetate in heptane, then by silica chromatography using isocratic elution with dichloromethane to give 2-(3-bromo-4-methoxyphenyl)-2-cyclopropyl-4-methyl-1H-imidazole-5(2H)-thione (1.780 g, 52% yield) : ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.53 (s, 1 H) 7.67 (d, 1 H) 7.48 (dd, 1 H) 7.14 (d, 1 H) 3.84 (s, 3 H) 2.23 (s, 3 H) 1.52 - 1.61 (m, 1 H) 0.43 - 0.55 (m, 2 H) 0.32 - 0.42 (m, 1 H) 0.15 - 0.24 (m, 1 H); MS (ES+) *m/z* 339, 341 $[M+H]^+$.

Example 59i

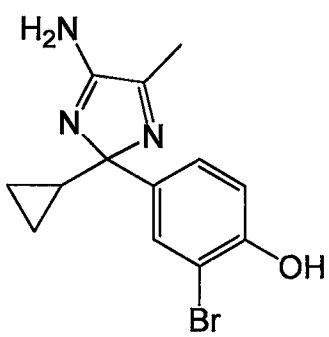
2-(3-Bromo-4-methoxyphenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine



2-(3-Bromo-4-methoxyphenyl)-2-cyclopropyl-4-methyl-1H-imidazole-5(2H)-thione (0.780 g, 2.30 mmol) and ammonia (7 N in MeOH, 10 mL, 70.00 mmol) were added to a microwave vial and irradiated in a microwave reactor at 110 °C for 1 h. The solvent was evaporated, ammonia (7 N in MeOH, 10 mL, 70.00 mmol) was added and the mixture was irradiated in a microwave reactor at 110 °C for 2 h. The solvent was evaporated, ammonia (7 N in MeOH, 10 mL, 70.00 mmol) was added and the mixture was irradiated in a microwave reactor at 110 °C for 1 h. This cycle was repeated three more times, then the reaction mixture was concentrated *in vacuo*. The product was purified by silica chromatography using 0% to 100% ethyl acetate in heptane to give 2-(3-bromo-4-methoxyphenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (0.486 g, 66% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.66 (d, 1 H) 7.52 (dd, 1 H) 7.02 (d, 1 H) 6.48 (s, 2 H) 3.81 (s, 3 H) 2.14 (s, 3 H) 1.43 (tt, 1 H) 0.23 - 0.33 (m, 2 H) 0.16 - 0.23 (m, 1 H) -0.07 - 0.01 (m, 1 H); MS (ES+) *m/z* 322, 324 $[M+H]^+$.

Example 60i

4-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-bromophenol

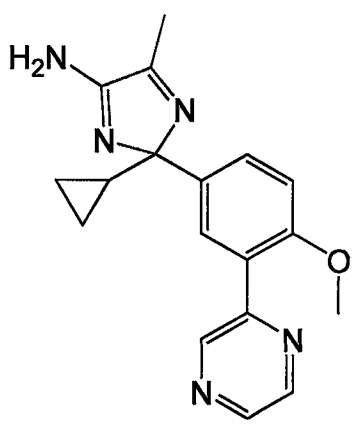


2-(3-Bromo-4-methoxyphenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (0.07 g, 0.22 mmol) was dissolved in dichloromethane (3.00 mL) and boron tribromide (0.144 mL, 1.52 mmol) was added. The reaction mixture was stirred at room temperature over night.

The reaction was quenched by dropwise addition of MeOH (2 mL). NH_4OH (28-30 wt% NH_3 in water, 1 mL) was added. The resulting mixture was stirred for 5 min. HCl was added dropwise until pH approximately 7. Additional dichloromethane was added and the organic layer was collected. The water phase was extracted with dichloromethane. NaCl was added and the water phase was extracted with acetonitrile (three times). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give crude 4-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-bromophenol (0.154 g) that was used as such in the next step: MS (ES+) *m/z* 308, 310 $[M+H]^+$.

Example 61i

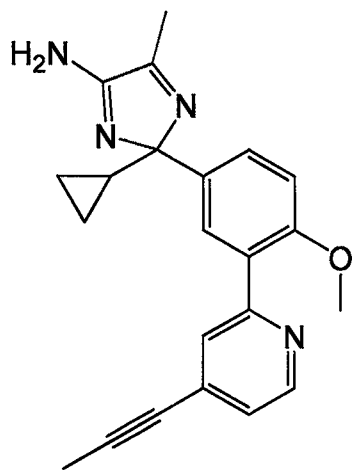
2-Cyclopropyl-2-(4-methoxy-3-(pyrazin-2-yl)phenyl)-5-methyl-2H-imidazol-4-amine



2-(Tributylstannyl)pyrazine (0.098 mL, 0.31 mmol), 2-(3-bromo-4-methoxyphenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (0.100 g, 0.31 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.036 g, 0.03 mmol) were dissolved in anhydrous DMF (2.00 mL) in a dry microwave vial under argon atmosphere. The mixture was irradiated in a microwave reactor for 30 min at 150 °C. The reaction mixture was filtered through a syringe filter and purified by prep-HPLC to give 2-cyclopropyl-2-(4-methoxy-3-(pyrazin-2-yl)phenyl)-5-methyl-2H-imidazol-4-amine (0.080 g, 46% yield): ^1H NMR (500 MHz, DMSO-d_6) δ ppm 9.07 (d, 1 H), 8.72 - 8.75 (m, 1 H), 8.54 (d, 1 H), 7.98 (d, 1 H), 7.67 (dd, 1 H), 7.12 (d, 1 H), 6.48 (br. s., 2 H), 3.85 (s, 3 H), 2.14 (s, 3 H), 1.43 - 1.50 (m, 1 H), 0.24 - 0.33 (m, 2 H), 0.17 - 0.24 (m, 1 H), -0.05 - 0.03 (m, 1 H) ; MS (ES+) *m/z* 322 $[M+H]^+$.

Example 62i

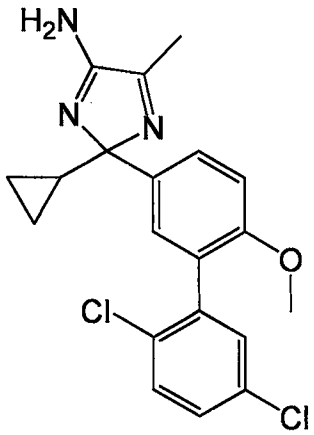
2-Cyclopropyl-2-(4-methoxy-3-(4-(prop-1-ynyl)pyridin-2-yl)phenyl)-5-methyl-2H-imidazol-4-amine



4-(Prop-1-ynyl)-2-(trimethylstannyl)pyridine (0.313 g, 1.12 mmol), 2-(3-bromo-4-methoxyphenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (0.120 g, 0.37 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.043 g, 0.04 mmol) were dissolved in anhydrous DMF (2.00 mL) in a dry microwave vial under argon atmosphere. The reaction mixture was irradiated in a microwave reactor for 30 min at 150 °C. The mixture was then filtered through a syringe filter and purified by prep-HPLC, then by silica chromatography using 0% to 10% (3.5 M ammonia in methanol) in dichloromethane to give 2-cyclopropyl-2-(4-methoxy-3-(4-(prop-1-ynyl)pyridin-2-yl)phenyl)-5-methyl-2H-imidazol-4-amine (0.016 g, 12 % yield) : ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.62 (dd, 1 H), 7.95 (d, 1 H), 7.75 (s, 1 H), 7.60 (dd, 1 H), 7.27 (dd, 1 H), 7.06 (d, 1 H), 6.43 (br. s., 2 H), 3.82 (s, 3 H), 2.14 (s, 3 H), 2.11 (s, 3 H), 1.41 - 1.49 (m, 1 H), 0.24 - 0.32 (m, 2 H), 0.15 - 0.23 (m, 1 H), -0.05 - 0.02 (m, 1 H); MS (ES+) *m/z* 359 $[M+H]^+$.

Example 63i

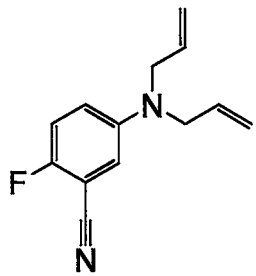
2-Cyclopropyl-2-(2',5'-dichloro-6-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-4-amine



2,5-Dichlorobenzeneboronic acid (62.2 mg, 0.33 mmol), 2-(3-bromo-4-methoxyphenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (70 mg, 0.22 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride (8.94 mg, 10.86 µmol), cesium carbonate (212 mg, 0.65 mmol) and DME:EtOH:Water 6:3:1 (3.00 mL) were put in a microwave vial and irradiated in a microwave reactor at 150 °C for 30 min. Additional 2,5-dichlorobenzeneboronic acid (41.5 mg, 0.22 mmol) was added and the resulting mixture was irradiated in a microwave reactor at 150 °C for 30 min. Additional [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride (8.94 mg, 10.86 µmol) was added and the resulting mixture was irradiated in a microwave reactor at 150 °C for 30 min. The reaction mixture was concentrated *in vacuo*. The residue was redissolved in dichloromethane and methanol, filtered and concentrated *in vacuo*. The product was purified by silica chromatography using 0% to 10% (3.5 M ammonia in methanol) in dichloromethane. The desired fractions were pooled and concentrated *in vacuo*. Impure fractions of the title compound were pooled and concentrated *in vacuo* and then purified by silica chromatography using 0% to 10% (3.5 M ammonia in methanol) in dichloromethane. All fractions containing the title compound were pooled and concentrated *in vacuo* to give 2-cyclopropyl-2-(2',5'-dichloro-6-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-4-amine (0.060 g, 72% yield, containing an unidentified biproduct): MS (ES-) *m/z* 387 $[M-H]^-$.

Example 64i

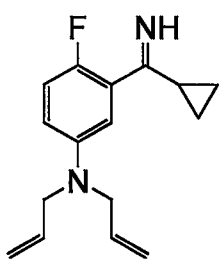
5-(Diallylamino)-2-fluorobenzonitrile



Allyl bromide (4.66 mL, 55.10 mmol), 5-amino-2-fluorobenzonitrile (3.00 g, 22.04 mmol) and sodium carbonate (0.942 mL, 22.48 mmol) were dissolved in ethanol (70.00 mL) and water (20.00 mL) and refluxed over night. The reaction mixture was allowed to cool to room temperature and the ethanol was then evaporated *in vacuo*. The remaining water mixture was extracted with diethyl ether (twice). The combined organic layers were passed through a phase separator and concentrated *in vacuo*. The product was purified by silica chromatography using 0% to 50% ethyl acetate in heptane to give 5-(diallylamino)-2-fluorobenzonitrile (3.31 g, 70% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.22 - 7.32 (m, 1 H), 6.91 - 7.04 (m, 2 H), 5.76 - 5.88 (m, 2 H), 5.08 - 5.22 (m, 4 H), 3.95 (d, 4 H); MS (ES+) *m/z* 217 $[M+H]^+$.

Example 65i

N,N-Diallyl-3-(cyclopropyl(imino)methyl)-4-fluoroaniline

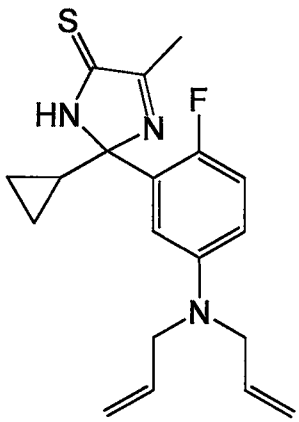


5-(Diallylamino)-2-fluorobenzonitrile (3.311 g, 15.31 mmol) and copper(I) bromide (0.110 g, 0.77 mmol) were dissolved in THF (25.0 mL) under argon. Cyclopropylmagnesium bromide (0.5 M in THF, 33.7 mL, 16.84 mmol) was added dropwise. The mixture was heated to 50 °C and stirred for 6.5 h. Additional cyclopropylmagnesium bromide (0.5 M in THF) (30.6 mL, 15.31 mmol) was added and the resulting mixture was stirred at 50 °C over night. The reaction was quenched by addition of methanol (15.0 mL) and then stirred for 10 min, and then the solvents were removed *in vacuo*. The residue was partitioned between water and dichloromethane (twice). The combined organic layers were

dried (Na_2SO_4), filtered through a pad of Celite and concentrated *in vacuo* to give crude N,N-diallyl-3-(cyclopropyl(imino)methyl)-4-fluoroaniline (4.04 g) that was used as such in the next step: MS (APCI+) *m/z* 259 $[M+H]^+$.

Example 66i

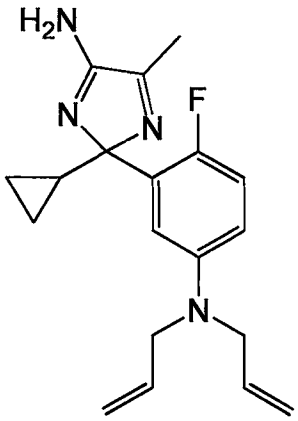
2-Cyclopropyl-2-(5-(diallylamino)-2-fluorophenyl)-4-methyl-1H-imidazole-5(2H)-thione



N,N-Diallyl-3-(cyclopropyl(imino)methyl)-4-fluoroaniline (4 g, 15.48 mmol) and 2-oxopropanethioamide (2.71 g, 26.32 mmol) were stirred in MeOH (50.0 mL) at 40 °C over night, then the mixture was concentrated *in vacuo*. The product was purified by silica chromatography using 0% to 40% ethyl acetate in heptane to give 2-cyclopropyl-2-(5-(diallylamino)-2-fluorophenyl)-4-methyl-1H-imidazole-5(2H)-thione (3.02 g, 57% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.21 (s, 1 H), 6.90 - 7.01 (m, 2 H), 6.63 (dt, 1 H), 5.83 (ddt, 2 H), 5.10 - 5.23 (m, 4 H), 3.91 (d, 4 H), 2.20 (s, 3 H), 1.77 (tt, 1 H), 0.52 (dqd, 2 H), 0.40 (dq, 1 H), 0.13 - 0.21 (m, 1 H); MS (ES-) *m/z* 342 $[M-H]^-$.

Example 67i

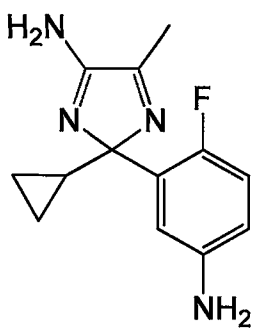
2-Cyclopropyl-2-(5-(diallylamino)-2-fluorophenyl)-5-methyl-2H-imidazol-4-amine



2-Cyclopropyl-2-(5-(diallylamino)-2-fluorophenyl)-4-methyl-1H-imidazole-5(2H)-thione (1.00 g, 2.91 mmol) and ammonia (7 N in MeOH, 13 mL, 91.00 mmol) were added to a microwave vial and irradiated in a microwave reactor at 110 °C for 1 h. The solvent was evaporated, ammonia (7 N in MeOH, 13 mL, 91.00 mmol) was added and the mixture irradiated in a microwave reactor at 110 °C for 1 h. This cycle (evaporation, addition of ammonia and irradiation) was repeated six more times, then the mixture was concentrated *in vacuo*. The produc twas purified by silica chromatography using 0% to 100% ethyl acetate in heptane to give 2-cyclopropyl-2-(5-(diallylamino)-2-fluorophenyl)-5-methyl-2H-imidazol-4-amine (0.734 g, 77% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 6.90 - 6.95 (m, 1 H), 6.83 (dd, 1 H), 6.42 - 6.53 (m, 3 H), 5.80 (ddt, 2 H), 5.09 - 5.19 (m, 4 H), 3.83 (d, 4 H), 2.12 (s, 3 H), 1.70 - 1.81 (m, 1 H), 0.26 - 0.36 (m, 2 H), 0.12 - 0.20 (m, 1 H), -0.12 - - 0.04 (m, 1 H); MS (ES-) *m/z* 325 $[M-H]^-$.

Example 68i

2-(5-Amino-2-fluorophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine

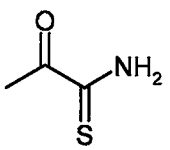


1,3-Dimethylbarbituric acid (0.580 g, 3.71 mmol) and

tetrakis(triphenylphosphine)palladium(0) (0.072 g, 0.06 mmol) were put in a microwave vial under argon. 2-Cyclopropyl-2-(5-(diallylamino)-2-fluorophenyl)-5-methyl-2H-imidazol-4-amine (0.202 g, 0.62 mmol) in dichloromethane (5.00 mL) was added. The resulting mixture was irradiated in a microwave reactor for 40 min at 100 °C, and then concentrated *in vacuo*. The residue was partitioned between aqueous sodium bicarbonate (sat.) and ethyl acetate . NaCl was added to the water phase, that was extracted with ethyl acetate (three times), and then with acetonitrile (three times), the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The produc twas purified by silica chromatography using 0% to 10% (3.5 M ammonia in methanol) in dichloromethane to give 2-(5-amino-2-fluorophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (0.044 g, 29% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 6.67 - 6.75 (m, 2 H), 6.42 (br. s., 2 H), 6.38 (dt, 1 H), 4.81 (s, 2 H), 2.12 (s, 3 H), 1.69 - 1.78 (m, 1 H), 0.24 - 0.36 (m, 2 H), 0.09 - 0.21 (m, 1 H), -0.16 - -0.03 (m, 1 H); MS (ES+) m/*z* 247 $[M+H]^+$.

Example 69i

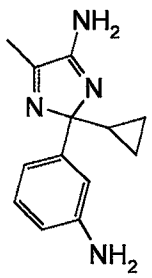
2-Oxopropanethioamide



A solution of acetyl cyanide (140 mL, 1764.24 mmol) in 2-methyltetrahydrofuran (850 mL) was stirred at -10 °C as hydrogen sulfide (Sigma-Aldrich lecture bottle) was bubbled through the solution. The addition of hydrogen sulfide was stopped after 15 min and to the stirred mixture, triethylamine (1.230 mL, 8.82 mmol) in 2-methyltetrahydrofuran (13 mL) was added slowly over 30 min (exothermic reaction). Hydrogen sulfide addition was continued for 3 h at 5 °C, 3 h at 10 °C and overnight at 15 °C. Nitrogen gas was bubbled though the solution for 30 min, followed by evaporation of the volatiles. To the residue was added a mixture of heptane (100 mL) and ethyl acetate (100 mL). A solid was filtered off (79 g, 43% yield) and the filtrate was purified by a short-plug silica gel chromatography, eluting with 50% ethylacetate in heptane to give 79 g (43% yield) of the title compound. Both crops (in total 158 g, 87% yield) contained the title product of adequate purity according to GC-MS: MS (ES+) *m/z* 104 [M+1].

Example 70i

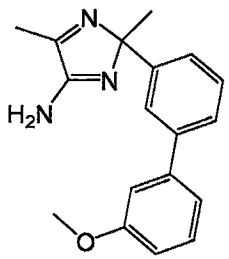
2-(3-Aminophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine



To a solution of 2-(3-bromophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (248 mg, 0.85 mmol) in dry dimethylsulfoxide (4 mL) in a microwave vial was added copper(I) iodide (32.3 mg, 0.17 mmol), trans-4-hydroxy-L-proline (44.5 mg, 0.34 mmol) and potassium carbonate (0.145 mL, 2.55 mmol). The vial was filled with argon and then ammonia (25% aqueous solution, 0.979 mL, 12.73 mmol) was added. The vial was sealed and heated in an oil-bath at 60 °C for 21 hours. LCMS analysis indicated low conversion so dimethylsulfoxide (1.0 mL), copper(I) iodide (32.3 mg, 0.17 mmol), trans-4-hydroxy-L-proline (44.5 mg, 0.34 mmol) and ammonia (25% aqueous solution, 1.0 mL, 1.3 mmol) was added and the heating continued at 60 °C for another ~90 hours. The reaction mixture was diluted with water and brine and the product extracted with EtOAc. The product was extracted with aqueous 1M HCl, the aqueous phase basified with saturated aqueous $NaHCO_3$ (pH ~9), the basic solution saturated with NaCl and the product extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated to give the title compound (157 mg, 81% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 6.87 (t, 1 H) 6.78 (t, 1 H) 6.72 (m, 1 H) 6.36 (m, 1 H) 6.32 (s, 2 H) 4.90 (s, 2 H) 2.11 (s, 3 H) 1.41 (m, 1 H) 0.26 (m, 2 H) 0.14 (m, 1 H) -0.07 (m, 1 H); MS (ES+) m/z 229 $[M+H]^+$.

Example 1

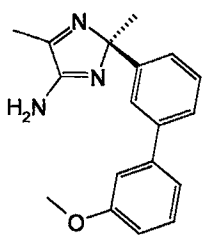
2-(3'-Methoxybiphenyl-3-yl)-2,5-dimethyl-2H-imidazol-4-amine



2-(3-Bromophenyl)-2,5-dimethyl-2H-imidazol-4-amine (41.4 mg, 0.16 mmol), 3-methoxyphenylboronic acid (28.4 mg, 0.19 mmol) and bis(triphenylphosphine)-palladium(II) chloride (10.92 mg, 0.02 mmol) were taken up in DME (2 mL) and water (1 mL). Sodium carbonate (1M in water) (0.389 mL, 0.39 mmol) was added and the reaction was heated to 80 °C for 2 h. Preparative HPLC yielded 21 mg (46.0% yield) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 (t, 1 H) 7.58 - 7.64 (m, 1 H) 7.46 - 7.51 (m, 1 H) 7.40 (t, 1 H) 7.35 (t, 1 H) 7.20 (ddd, 1 H) 7.15 (dd, 1 H) 6.89 (ddd, 1 H) 3.87 (s, 3 H) 2.29 (s, 3 H) 1.74 (s, 3 H); MS (ES+) *m/z* 294 $[M+H]^+$.

Example 2

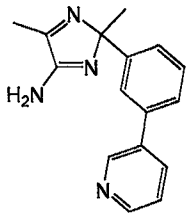
(R)-2-(3'-Methoxybiphenyl-3-yl)-2,5-dimethyl-2H-imidazol-4-amine



Chromatographic separation of the enantiomers of 2-(3'-Methoxybiphenyl-3-yl)-2,5-dimethyl-2H-imidazol-4-amine. 2-(3'-Methoxybiphenyl-3-yl)-2,5-dimethyl-2H-imidazol-4-amine (15 mg, 0.05 mmol) was dissolved in methanol (1 mL) and the resulting solution was injected on a Chiralpak AD column (21.2 x 250 mm), using methanol/CO_2 (25:75) + 0.1% diethylamine as eluent at a flow rate of 50 mL/min. The title compound was the first to elute and was concentrated *in vacuo* to yield 5.1 mg (34% yield): ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 7.69 (s, 1 H) 7.45 (t, 2 H) 7.27 - 7.36 (m, 2 H) 7.13 (d, 1 H) 7.10 (d, 1 H) 6.87 (dd, 1 H) 3.81 (s, 3 H) 2.27 (s, 3 H) 1.66 (s, 3 H); MS (ES+) *m/z* 294 $[M+H]^+$.

Example 3

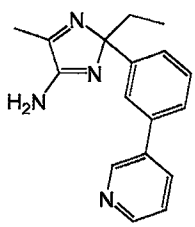
2,5-Dimethyl-2-(3-(pyridin-3-yl)phenyl)-2H-imidazol-4-amine



2-(3-Bromophenyl)-2,5-dimethyl-2H-imidazol-4-amine (40 mg, 0.15 mmol), pyridin-3-ylboronic acid (36.9 mg, 0.30 mmol) and bis(triphenylphosphine)palladium(II) chloride (10.55 mg, 0.02 mmol) were taken up in DME (1 mL) and water (0.5 mL). Sodium carbonate (1M in water) (0.376 mL, 0.38 mmol) was added and the reaction was heated to 80 °C for 2 h. Preparative HPLC yielded 30.1 mg (61.7% yield) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.85 (d, 1 H) 8.58 (d, 1 H) 7.92 (dd, 1 H) 7.81 (s, 1 H) 7.63 (d, 1 H) 7.47 (dt, 2 H) 7.37 (dd, 1 H) 2.32 (s, 3 H) 1.76 (s, 3 H); MS (ES+) *m/z* 265 $[M+H]^+$.

Example 4

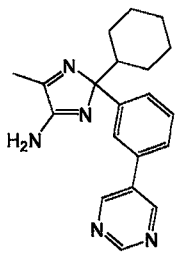
2-Ethyl-5-methyl-2-(3-(pyridin-3-yl)phenyl)-2H-imidazol-4-amine



2-(3-Bromophenyl)-2-ethyl-5-methyl-2H-imidazol-4-amine (8.8 mg, 0.03 mmol), pyridin-3-ylboronic acid (7.72 mg, 0.06 mmol) and bis(triphenylphosphine)palladium(II) chloride (4.41 mg, 6.28 µmol) were taken up in DME (1 mL) and water (0.5 mL). Sodium carbonate (1M in water) (0.079 mL, 0.08 mmol) was added and the reaction was heated to 80 °C for 2 h. Preparative HPLC yielded 6 mg (56% yield) of the title compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.88 (d, 1 H) 8.60 (dd, 1 H) 7.94 (dt, 1 H) 7.83 (s, 1 H) 7.63 (d, 1 H) 7.50 - 7.54 (m, 1 H) 7.43 - 7.49 (m, 1 H) 7.38 (dd, 1 H) 6.82 (br. s., 2 H) 2.33 (s, 3 H) 2.13 - 2.23 (m, 1 H) 2.01 - 2.09 (m, 1 H) 0.79 (t, 3 H); MS (ES+) *m/z* 279 $[M+H]^+$.

Example 5

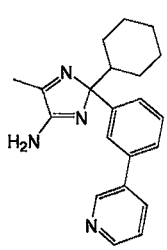
2-Cyclohexyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine



2-(3-Bromophenyl)-2-cyclohexyl-5-methyl-2H-imidazol-4-amine (60 mg, 0.18 mmol), pyrimidin-5-ylboronic acid (44.5 mg, 0.36 mmol) and bis(triphenylphosphine)-palladium(II) chloride (25.2 mg, 0.04 mmol) were taken up in DME (2 mL) and water (1 mL). Sodium carbonate (1M in water) (0.449 mL, 0.45 mmol) was added and the reaction was heated to 80 °C for 2 h. Preparative HPLC yielded 39.9 mg (67% yield) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.20 (s, 1 H) 8.98 (s, 2 H) 7.84 (s, 1 H) 7.67 - 7.76 (m, 1 H) 7.48 (d, 2 H) 5.19 (br. s., 2 H) 2.31 (s, 3 H) 2.05 - 2.15 (m, 1 H) 1.42 - 1.76 (m, 5 H) 0.86 - 1.26 (m, 5 H); MS (ES+) *m/z* 334 $[M+H]^+$.

Example 6

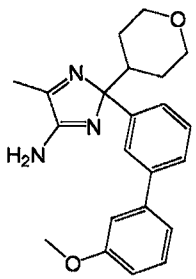
2-Cyclohexyl-5-methyl-2-(3-(pyridin-3-yl)phenyl)-2H-imidazol-4-amine



2-(3-Bromophenyl)-2-cyclohexyl-5-methyl-2H-imidazol-4-amine (60 mg, 0.18 mmol), pyridin-3-ylboronic acid (44.1 mg, 0.36 mmol) and bis(triphenylphosphine)palladium(II) chloride (25.2 mg, 0.04 mmol) were taken up in DME (2 mL) and water (1 mL). Sodium carbonate (1M in water) (0.449 mL, 0.45 mmol) was added and the reaction was heated to 80 °C for 2 h. Preparative HPLC yielded 27.9 mg (47% yield) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.87 (d, 1 H) 8.58 (dd, 1 H) 7.92 (ddd, 1 H) 7.84 (s, 1 H) 7.66 (d, 1 H) 7.46 - 7.52 (m, 1 H) 7.40 - 7.46 (m, 1 H) 7.35 (dd, 1 H) 5.50 (br. s., 2 H) 2.30 (s, 3 H) 2.06 - 2.17 (m, 1 H) 1.42 - 1.77 (m, 5 H) 0.86 - 1.25 (m, 5 H); MS (ES+) *m/z* 333 $[M+H]^+$.

Example 7

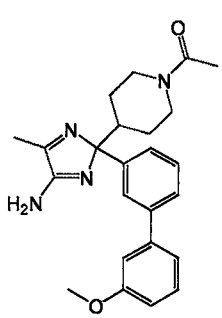
2-(3'-Methoxybiphenyl-3-yl)-5-methyl-2-(tetrahydro-2H-pyran-4-yl)-2H-imidazol-4-amine



To a solution of zinc iodide (646 mg, 2.02 mmol) in THF (10 mL) at 0 °C was added methylmagnesium bromide (3M in diethyl ether) (0.674 mL, 2.02 mmol). To the formed slurry was then added bis(triphenylphosphine)palladium(II) chloride (28.4 mg, 0.04 mmol) followed by 2-(3'-methoxybiphenyl-3-yl)-5-(methylthio)-2-(tetrahydro-2H-pyran-4-yl)-2H-imidazol-4-amine (80 mg, 0.20 mmol) in THF (5 mL). The reaction mixture was stirred at 80 °C for 3 h. MeOH was added to quench the reaction. Sat. aq. NH_4Cl solution was added and the mixture was extracted with with DCM. The combined organic phases were dried over $MgSO_4$, filtered and the solvent evaporated. Preparative HPLC yielded 18.4 mg (25% yield) of the title compound: ^{1}H NMR (400 MHz, MeOH) δ ppm 7.79 (s, 1 H) 7.59 - 7.68 (m, 1 H) 7.47 - 7.58 (m, 3 H) 7.38 (t, *J*=7.83 Hz, 1 H) 7.33 (t, *J*=7.83 Hz, 1 H) 7.18 (d, *J*=7.83 Hz, 1 H) 7.15 (d, *J*=2.02 Hz, 1 H) 6.90 (dd, *J*=8.08, 2.02 Hz, 1 H) 3.87 (d, *J*=11.37 Hz, 2 H) 3.84 (s, 3 H) 3.24 - 3.37 (m, 2 H) 2.35 - 2.47 (m, 1 H) 2.32 (s, 3 H) 1.22 - 1.43 (m, 4 H); MS (ES+) *m/z* 364 $[M+H]^+$.

Example 8

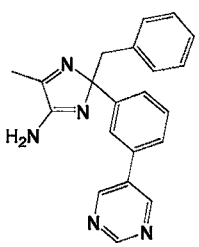
1-(4-(4-Amino-2-(3'-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)piperidin-1-yl)ethanone



tert-Butyl 4-(4-amino-2-(3'-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)piperidine-1-carboxylate (15.7 mg, 0.03 mmol) was dissolved in DCM (2 mL). Trifluoroacetic acid (1 ml, 13 mmol) was added and the reaction was stirred at room temperature for 1 h. The solvent and excess reagent were evaporated. The residue was dissolved in DCM (2 mL) and triethylamine (11.35 µl, 0.08 mmol). Acetic anhydride (3.84 µl, 0.04 mmol) was added and the reaction was stirred for 16 h. The solvent was evaporated and preparative HPLC yielded 12.2 mg (77% yield) of the title compound: ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 7.80 (br. s., 1 H) 7.53 (d, 2 H) 7.39 (t, 1 H) 7.34 (t, 1 H) 7.18 (d, 1 H) 7.16 (s, 1 H) 6.91 (dd, 1 H) 4.49 (d, 1 H) 3.79 - 3.92 (m, 4 H) 2.90 - 3.06 (m, 1 H) 2.39 - 2.54 (m, 2 H) 2.33 (br. s., 3 H) 2.03 (s, 3 H) 1.36 - 1.62 (m, 2 H) 1.25 (d, 1 H) 0.99 - 1.17 (m, 1 H); MS (ES+) *m/z* 405 $[M+H]^+$.

Example 9

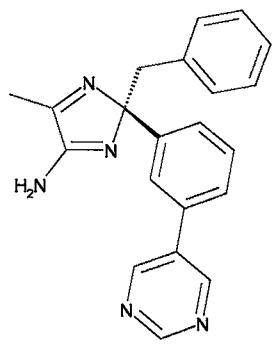
2-Benzyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine



2-Benzyl-2-(3-bromophenyl)-5-methyl-2H-imidazol-4-amine (66.5 mg, 0.19 mmol), pyrimidin-5-ylboronic acid (48.2 mg, 0.39 mmol) and bis(triphenylphosphine)-palladium(II) chloride (27.3 mg, 0.04 mmol) were taken up in DME (1 mL) and water (0.5 mL). Sodium carbonate (1M in water) (0.486 mL, 0.49 mmol) was added and the reaction was heated to 80 °C for 2 h. The reaction mixture was extracted with DCM. The combined organic phases were dried over $MgSO_4$, filtered and the solvent evaporated. Preparative HPLC yielded 30 mg (45% yield) of the title compound: MS (ES+) *m/z* 342 $[M+H]^+$.

Example 10

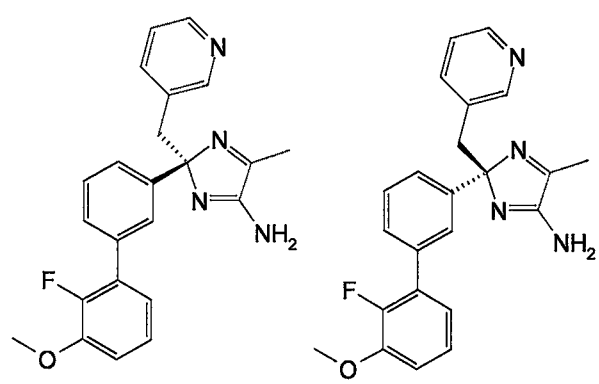
(R)- 2-Benzyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine



Chromatographic separation of the enantiomers of 2-benzyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine. 2-Benzyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine (29.6 mg, 0.087 mmol) was dissolved in methanol (2.7 mL) and the resulting solution was injected on a Chiralcel OJ column (21.2 x 250 mm), using methanol/CO_2 (18:82) + 0.1% diethylamine as eluent at a flow rate of 50 mL/min. The title compound was the second to elute and was concentrated *in vacuo* to yield 7.5 mg (26% yield): ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 9.14 (s, 1 H) 9.05 (s, 2 H) 7.89 (t, 1 H) 7.76 (dt, 1 H) 7.62 - 7.67 (m, 1 H) 7.52 (t, 1 H) 7.11 - 7.20 (m, 3 H) 7.01 - 7.08 (m, 2 H) 3.40 - 3.49 (m, 1 H) 3.33 - 3.40 (m, 1 H) 2.07 (s, 3 H); MS (ES+) *m/z* 342 $[M+H]^+$.

Example 11

(R)- and (S)- 2-(2'-fluoro-3'-methoxybiphenyl-3-yl)-5-methyl-2-(pyridin-3-ylmethyl)-2H-imidazol-4-amine



2-(3-Bromophenyl)-5-methyl-2-(pyridin-3-ylmethyl)-2H-imidazol-4-amine (100 mg, 0.29 mmol), 2-fluoro-3-methoxybenzeneboronic acid (54.5 mg, 0.32 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride (11.98 mg, 0.01 mmol), potassium

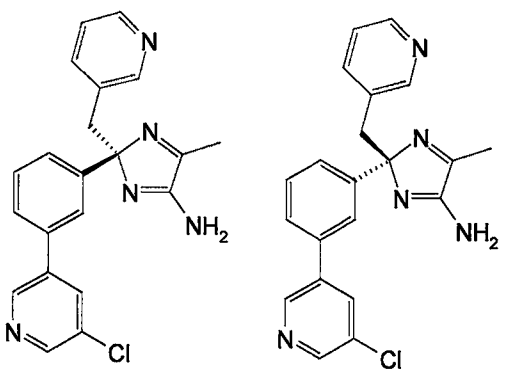
carbonate (2M aqueous solution, 0.364 mL, 0.73 mmol) and dioxane (1 mL) were mixed in a vial and heated in a microwave reactor at 130 °C for 15 min. The mixture was filtered and purified by preparative HPLC. The product was dissolved in MeOH and injected on a Chiralpak AD-H column (4.6 x 250 mm), using EtOH+DEA /CO_2 (30:70) as eluent at a flow rate of 2 mL/min. Detection was monitored at 220 nm and the two isomers were collected and concentrated *in vacuo* to yield:

Isomer 1, example 11a: 8 mg (7% yield) with unknown absolute configuration was collected: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.30 (dd, 1 H) 8.14 (d, 1 H) 7.67 (s, 1 H) 7.57 - 7.65 (m, 1 H) 7.33 - 7.41 (m, 3 H) 7.12 - 7.24 (m, 3 H) 6.87 - 6.97 (m, 1 H) 6.38 (br. s., 2 H) 3.87 (s, 3 H) 3.10 - 3.25 (m, 2 H) 2.01 (s, 3 H); MS (ES+) *m/z* 389 $[M+1]^+$.

Isomer 2, example 11b: 8 mg (7% yield) with unknown absolute configuration was collected: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.30 (dd, 1 H) 8.14 (d, 1 H) 7.67 (s, 1 H) 7.58 - 7.64 (m, 1 H) 7.32 - 7.41 (m, 3 H) 7.11 - 7.25 (m, 3 H) 6.86 - 6.97 (m, 1 H) 6.38 (br. s., 2 H) 3.87 (s, 3 H) 3.11 - 3.24 (m, 2 H) 2.01 (s, 3 H); MS (ES+) *m/z* 389 $[M+1]^+$.

Example 12

(R)- and (S)- 2-(3-(5-Chloropyridin-3-yl)phenyl)-5-methyl-2-(pyridin-3-ylmethyl)-2H-imidazol-4-amine



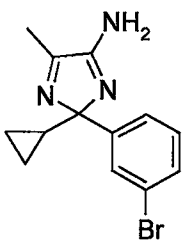
The racemate of the title compounds were synthesized as described in Example 11 in 20% yield starting from 2-(3-bromophenyl)-5-methyl-2-(pyridin-3-ylmethyl)-2H-imidazol-4-amine and 5-chloropyridine-3-boronic acid. The crude product was dissolved in MeOH and injected on a Chiralpak AD-H column (4.6 x 250 mm), using EtOH+DEA /CO_2 (40:60) as eluent at a flow rate of 2 mL/min. Detection was monitored at 220 nm and the two isomers were collected and concentrated *in vacuo* to yield:

Isomer 1, example 12a: 15 mg with unknown absolute configuration was collected: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.76 (d, 1 H) 8.63 (d, 1 H) 8.31 (dd, 1 H) 8.11 - 8.19 (m, 2 H) 7.83 - 7.90 (m, 1 H) 7.62 (dd, 2 H) 7.35 - 7.45 (m, 2 H) 7.17 (dd, 1 H) 6.41 (br. s., 2 H) 3.17 - 3.29 (m, 2 H) 2.02 (s, 3 H); MS (ES+) *m/z* 376, 378 $[M+1]^+$.

Isomer 2, example 12b: 15 mg with unknown absolute configuration was collected: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.76 (d, 1 H) 8.63 (d, 1 H) 8.31 (dd, 1 H) 8.10 - 8.20 (m, 2 H) 7.86 (t, 1 H) 7.62 (dd, 2 H) 7.35 - 7.45 (m, 2 H) 7.17 (dd, 1 H) 6.41 (br. s., 2 H) 3.16 - 3.29 (m, 2 H) 2.02 (s, 3 H); MS (ES+) *m/z* 376, 378 $[M+1]^+$.

Example 13

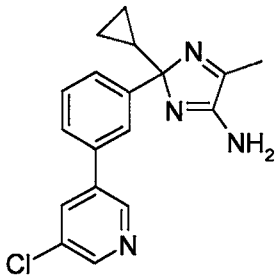
2-(3-Bromophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine



2-(3-Bromophenyl)-2-cyclopropyl-4-methyl-1H-imidazole-5(2H)-thione (1.2 g, 3.88 mmol) and ammonia (7N in MeOH, 38.8 mL, 271.65 mmol) was heated to 45 °C o.n. The solvent was evaporated, ammonia (7N in MeOH, 38.8 mL, 271.65 mmol) was added and the mixture were heated to 45 °C for 8 h. This procedure were repeated 3 times and after final evaporation of the solvent, the title compound was isolated by chromatography (0-60% EtOAc in n-heptane) to give 1.02 g (90% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.68 (s, 1 H) 7.56 - 7.61 (m, 1 H) 7.39 - 7.45 (m, 1 H) 7.26 (t, 1 H) 6.53 (br. s., 2 H) 2.15 (s, 3 H) 1.45 - 1.52 (m, 1 H) 0.26 - 0.35 (m, 2 H) 0.17 - 0.25 (m, 1 H) -0.06 - 0.02 (m, 1 H). MS (ES) *m/z* 292, 294 $[M+1]^+$.

Example 14

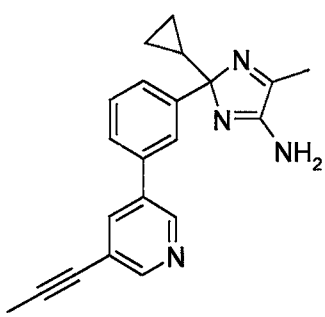
2-(3-(5-Chloropyridin-3-yl)phenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine



5-Chloropyridin-3-ylboronic acid (67.9 mg, 0.43 mmol), 2-(3-bromophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (90 mg, 0.31 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride (12.67 mg, 0.02 mmol) and potassium carbonate (2M in water, 0.385 mL, 0.77 mmol) were dissolved in dioxane (2 mL) and heated to 150 °C for 20 min using MW. After filtration and removal of solvents, the title compound was isolated using preparative HPLC to give 52 mg (52% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.78 (s, 1 H) 8.62 - 8.65 (m, 1 H) 8.15 (s, 1 H) 7.88 (s, 1 H) 7.59 - 7.68 (m, 2 H) 7.43 (t, 1 H) 6.50 (br. s., 2 H) 2.16 (s, 3 H) 1.56 - 1.64 (m, 1 H) 0.27 - 0.39 (m, 2 H) 0.17 - 0.26 (m, 1 H) -0.01 - 0.07 (m, 1 H). MS (ES) *m/z* 325 $[M+1]^+$.

Example 15

2-Cyclopropyl-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-4-amine

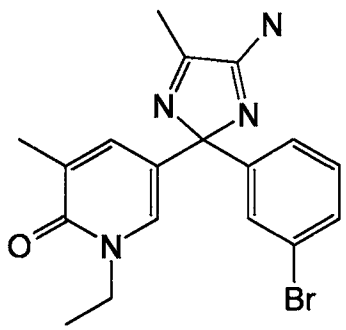


The title compound was synthesized as described for Example 14 in 40% yield starting from 5-(prop-1-ynyl)pyridin-3-ylboronic acid (86 mg, 0.53 mmol) and 2-(3-bromophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (78 mg, 0.27 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.73 - 8.77 (m, 1 H) 8.58 (s, 1 H) 7.98 (s, 1 H) 7.85 (s, 1 H) 7.64 (d, 1 H) 7.59 (d, 1 H) 7.41 (t, 1 H) 6.50 (br. s., 2 H) 2.16 (s, 3 H) 2.12 (s, 3 H) 1.55 - 1.62 (m, 1

H) 0.27 - 0.39 (m, 2 H) 0.16 - 0.26 (m, 1 H) -0.02 - 0.07 (m, 1 H). MS (ES) *m/z* 329 $[M+1]^+$.

Example 16

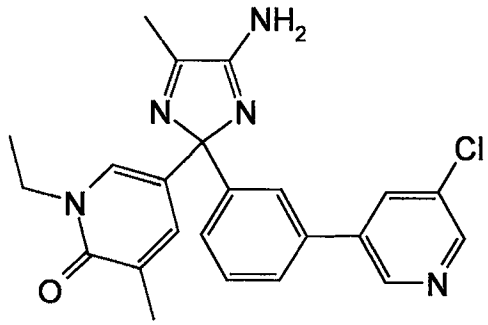
5-(4-Amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-3-methylpyridin-2(1H)-one



Sodium hydride (0.042 mL, 1.25 mmol) was added in one portion at 0 °C to a solution of 5-(4-amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-3-methylpyridin-2(1H)-one (450 mg, 1.25 mmol) in dry N,N-dimethylformamide (10 mL) under argon. The reaction was stirred at 0 °C for 5 minutes and then at rt for 20 minutes. The reaction was cooled to 0 °C and a solution of iodoethane (0.121 mL, 1.50 mmol) in dry N,N-dimethylformamide (3 mL) was added dropwise. LCMS indicated almost full conversion after 3.5 hours at 0 °C. The reaction was quenched by addition of MeOH (1.0 mL) and the reaction was stirred for 10 minutes at rt before evaporation of the solvents at reduced pressure. Remaining N,N-dimethylformamide was removed by co-evaporation with toluene. The residue was partitioned between DCM and saturated aqueous $NaHCO_3$, the phases were separated and the aqueous layer extracted with DCM. The organic phases were combined, dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on silica using a gradient from 0-10% MeOH in DCM gave the title compound (172 mg, (36% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.59 (t, 1 H) 7.50 (m, 2 H) 7.41 (ddd, 1 H) 7.35 (dd, 1 H) 7.25 (t, 1 H) 6.72 (br. s., 2 H) 3.88 (q, 2 H) 3.17 (d, 1 H) 2.23 (s, 2 H) 1.93 (s, 2 H) 1.16 (t, 3 H); MS (ES+) m/z 387, 389 $[M+H]^+$.

Example 17

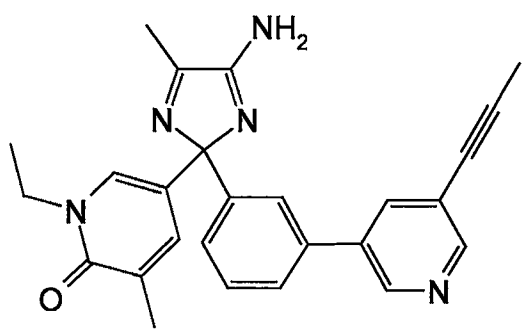
5-(4-Amino-2-(3-(5-chloropyridin-3-yl)phenyl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one



A mixture of 5-(4-amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one (65.0 mg, 0.17 mmol), 5-chloropyridine-3-boronic acid (31.7 mg, 0.20 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)chloride (6.90 mg, 8.39 μmol), potassium carbonate (aqueous 2M) (0.168 mL, 0.34 mmol) and dioxane (2.0 mL) were heated in a microwave synthesizer at 130 °C for 15 minutes. The solvent was evaporated, the residue taken up in a MeOH/DMSO mixture and purified by preparative HPLC to give the title compound (20 mg, 28% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.77 (d, 1 H) 8.63 (d, 1 H) 8.15 (t, 1 H) 7.81 (t, 1 H) 7.58-7.64 (m, 2 H) 7.56 (d, 1 H) 7.46 (dd, 1 H) 7.42 (m, 1 H) 6.68 (s, 2 H) 3.88 (q, 2 H) 2.25 (s, 3 H) 1.93 (s, 3 H) 1.16 (t, 3 H); MS (ES+) m/z 420 $[M+H]^+$.

Example 18

5-(4-Amino-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one

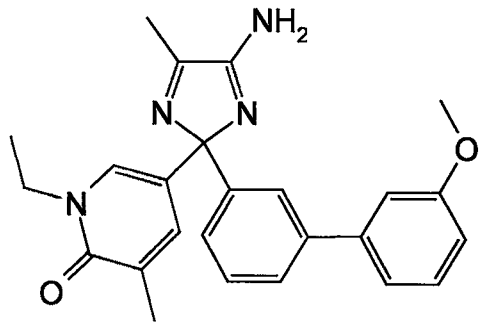


The title compound was synthesized as described for Example 17 starting from 5-(4-amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one

(65.0 mg, 0.17 mmol) and 5-(prop-1-ynyl)pyridin-3-ylboronic acid (40.5 mg, 0.25 mmol) to give the title compound (19 mg, 27% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.73 (d, 1 H) 8.57 (d, 1 H) 7.98 (t, 1 H) 7.78 (t, 1 H) 7.53 - 7.63 (m, 3 H) 7.46 (dd, 1 H) 7.36 - 7.43 (m, 1 H) 6.68 (s, 2 H) 3.88 (q, 2 H) 2.24 (s, 3 H) 2.11 (s, 3 H) 1.93 (s, 3 H) 1.16 (t, 3 H); MS (ES+) m/z 424 $[M+H]^+$.

Example 19

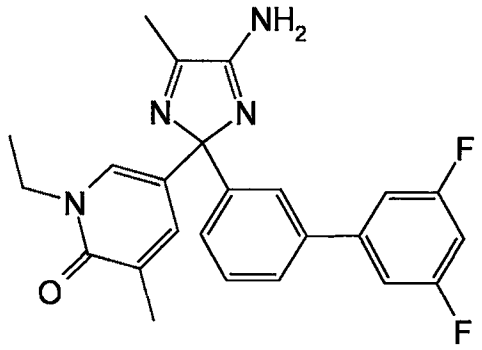
5-(4-Amino-2-(3'-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one



The title compound was synthesized as described for Example 17, from 5-(4-amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one (75 mg, 0.19 mmol) and 3-methoxyphenylboronic acid (35.3 mg, 0.23 mmol), with the exception that to achieve full conversion another portion of 3-methoxyphenylboronic acid (14.71 mg, 0.10 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)chloride (3.98 mg, 4.84 μmol) was added and the reaction heated for another 10 minutes at 130 °C. The title compound was afforded (48 mg, 60% yield, containing 10mol% MeOH): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.71 (t, 1 H) 7.54 (d, 1 H) 7.49 (m, 2 H) 7.42 (dd, 1 H) 7.37 (dt, 2 H) 7.12 (m, 1 H) 7.07 (m, 1 H) 6.94 (m, 1 H) 6.67 (br. s, 2 H) 4.10 (q, 0.2 H. MeOH) 3.88 (q, 2 H) 3.81 (s, 3 H) 3.17 (d, 0.3 H, MeOH) 2.24 (s, 3 H) 1.93 (s, 3 H) 1.16 (t, 3 H); MS (ES+) m/z 415 $[M+H]^+$.

Example 20

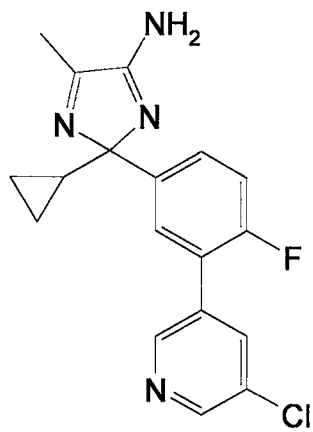
5-(4-Amino-2-(3',5'-difluorobiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one



The title compound was synthesized as described for Example 17 starting from 5-(4-amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one (75 mg, 0.19 mmol) and 3,5-difluorophenylboronic acid (36.7 mg, 0.23 mmol) to afford 57 mg (70 % yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.76 (t, 1 H) 7.53 - 7.61 (m, 3 H) 7.44 (dd, 1 H) 7.39 (t, 1 H) 7.33 (m, 2 H) 7.24 (tt, 1 H) 6.68 (br. s, 2 H) 3.88 (m, 2 H) 2.24 (s, 3 H) 1.93 (s, 3 H) 1.16 (t, 3 H); MS (ES+) m/z 421 $[M+H]^+$.

Example 21

2-(3-(5-Chloropyridin-3-yl)-4-fluorophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine

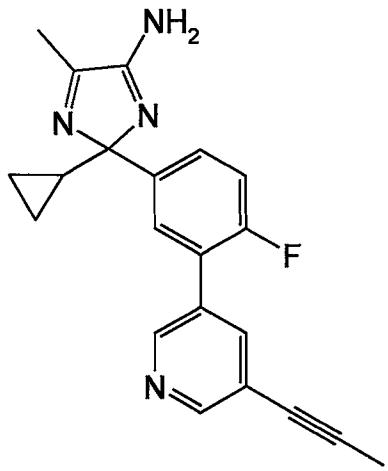


To a microwave vial was added 5-chloropyridin-3-ylboronic acid (51.9 mg, 0.33 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (9.61 mg, 0.01 mmol) and potassium carbonate (2M in water, 0.294 mL, 0.59 mmol), and then 2-(3-bromo-4-fluorophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (73.0 mg, 0.24 mmol) in dioxane (2 mL). The reaction vessel was sealed and heated at 150 °C for 20 min in a microwave reactor. After cooling, the reaction mixture was filtered and concentrated. The residue was taken up in MeOH, filtered and purified by prep HPLC to

yield 35 mg (43% yield) of the title compound: 1H NMR (500 MHz, DMSO-d_6) δ ppm 8.65 - 8.69 (m, 2 H) 8.08 - 8.12 (m, 1 H) 7.70 - 7.74 (m, 1 H) 7.64 - 7.70 (m, 1 H) 7.25 - 7.33 (m, 1 H) 6.52 (s, 2 H) 2.15 (s, 3 H) 1.57 (tt, 1 H) 0.28 - 0.37 (m, 2 H) 0.17 - 0.26 (m, 1 H) -0.04 - 0.06 (m, 1 H) ; MS (ES+) m/z 343 $[M+H]^+$.

Example 22

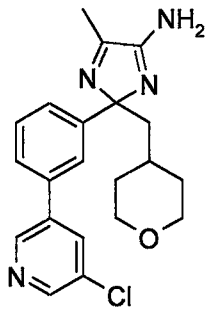
2-Cyclopropyl-2-(4-fluoro-3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-5-methyl-2H-imidazol-4-amine



The title compound 24 mg (33% yield) was prepared from 2-(3-bromo-4-fluorophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (65.0 mg, 0.21 mmol), and 5-(prop-1-ynyl)pyridin-3-ylboronic acid (67.5 mg, 0.42 mmol), according to a similar procedure as that described for Example 21: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.64 (s, 1 H) 8.61 (d, 1 H) 7.91 (d, 1 H) 7.69 (dd, 1 H) 7.62 - 7.67 (m, 1 H) 7.28 (dd, 1 H) 6.51 (br. s., 2 H) 2.15 (s, 3 H) 2.11 (s, 3 H) 1.51 - 1.62 (m, 1 H) 0.27 - 0.41 (m, 2 H) 0.14 - 0.27 (m, 1 H) - 0.04 - 0.10 (m, 1 H); MS (ES+) m/z 347 $[M+H]^+$.

Example 23

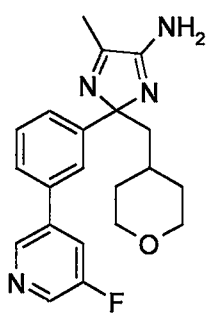
2-(3-(5-Chloropyridin-3-yl)phenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine



The title compound was synthesized as described for Example 14 in 61% yield starting from 5-chloropyridin-3-ylboronic acid (46.7 mg, 0.30 mmol) and 2-(3-bromophenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine (80 mg, 0.23 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.78 (d, 1 H) 8.63 (d, 1 H) 8.16 (t, 1 H) 7.86 (t, 1 H) 7.59 - 7.65 (m, 2 H) 7.42 (t, 1 H) 6.45 (br. s., 2 H) 3.63 - 3.73 (m, 2 H) 3.06 - 3.16 (m, 2 H) 2.16 (s, 3 H) 1.91 - 1.96 (m, 1 H) 1.67 - 1.74 (m, 1 H) 1.46 - 1.53 (m, 1 H) 1.37 - 1.44 (m, 1 H) 1.25 - 1.35 (m, 1 H) 1.00 - 1.14 (m, 2 H); MS (ES) *m/z* 383 $[M+1]^+$.

Example 24

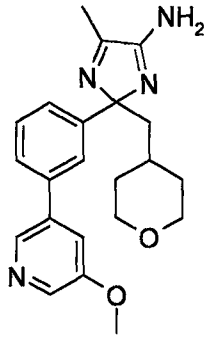
2-(3-(5-Fluoropyridin-3-yl)phenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine



The title compound was synthesized as described for Example 14 in 38% yield starting from 5-fluoropyridin-3-ylboronic acid (41.8 mg, 0.30 mmol) and 2-(3-bromophenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine (80mg, 0.23 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.71 (t, 1 H) 8.58 (d, 1 H) 7.96 - 8.01 (m, 1 H) 7.87 (t, 1 H) 7.59 - 7.65 (m, 2 H) 7.42 (t, 1 H) 6.45 (br. s., 2 H) 3.64 - 3.73 (m, 2 H) 3.07 - 3.16 (m, 2 H) 2.16 (s, 3 H) 1.91 - 1.96 (m, 1 H) 1.67 - 1.74 (m, 1 H) 1.46 - 1.53 (m, 1 H) 1.37 - 1.45 (m, 1 H) 1.25 - 1.36 (m, 1 H) 1.00 - 1.14 (m, 2 H); MS (ES) *m/z* 367 $[M+1]^+$.

Example 25

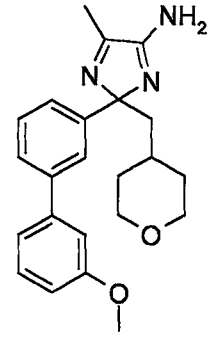
2-(3-(5-Methoxypyridin-3-yl)phenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine



The title compound was synthesized as described for Example 14 in 47% yield starting from 5-methoxypyridin-3-ylboronic acid (45.4 mg, 0.30 mmol) and 2-(3-bromophenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine (80mg, 0.23 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.32 (d, 1 H) 8.23 (d, 1 H) 7.76 (t, 1 H) 7.48 - 7.56 (m, 2 H) 7.43 - 7.47 (m, 1 H) 7.34 (t, 1 H) 6.38 (br. s., 2 H) 3.85 (s, 3 H) 3.56 - 3.67 (m, 2 H) 3.00 - 3.10 (m, 2 H) 2.10 (s, 3 H) 1.83 - 1.89 (m, 1 H) 1.59 - 1.66 (m, 1 H) 1.41 - 1.48 (m, 1 H) 1.31 - 1.38 (m, 1 H) 1.13 - 1.30 (m, 1 H) 0.94 - 1.07 (m, 2 H); MS (ES) *m/z* 379 $[M+1]^+$.

Example 26

2-(3'-Methoxybiphenyl-3-yl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine

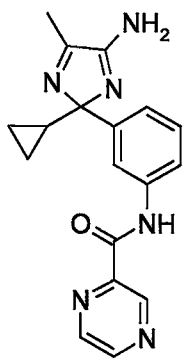


The title compound was synthesized as described for Example 14 in 52% yield starting from 3-methoxyphenylboronic acid (45.1 mg, 0.30 mmol) and 2-(3-bromophenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine (80mg, 0.23 mmol):

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.79 (t, 1 H) 7.55 (d, 1 H) 7.49 (d, 1 H) 7.32 - 7.41 (m, 2 H) 7.14 (d, 1 H) 7.07 - 7.11 (m, 1 H) 6.92 - 6.97 (m, 1 H) 6.43 (br. s., 2 H) 3.82 (s, 3 H) 3.63 - 3.72 (m, 2 H) 3.06 - 3.15 (m, 2 H) 2.16 (s, 3 H) 1.90 - 1.92 (m, 1 H) 1.63 - 1.69 (m, 1 H) 1.46 - 1.55 (m, 1 H) 1.38 - 1.44 (m, 1 H) 1.27 - 1.37 (m, 1 H) 0.99 - 1.14 (m, 2 H); MS (ES) *m/z* 378 $[M+1]^+$.

Example 27

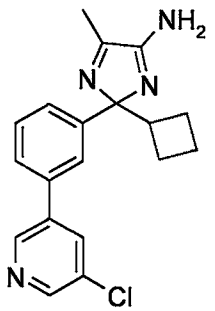
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)phenyl)pyrazine-2-carboxamide



Pyrazine-2-carboxamide (63.2 mg, 0.51 mmol), 2-(3-bromophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (50 mg, 0.17 mmol), palladium(II) acetate (3.84 mg, 0.02 mmol), cesium carbonate (112 mg, 0.34 mmol) and Xantphos (14.85 mg, 0.03 mmol) were dissolved in THF (2 mL) and heated to 150 °C for 1 h using MW. After filtration and removal of solvents *in vacuo*, were the title compound isolated using preparative HPLC to give 33mg (58% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.65 (s, 1 H), 9.29 (d, 1 H), 8.92 (d, 1 H), 8.81 (m, 1 H), 8.13 (t, 1 H), 7.69 (m, 1 H), 7.35 (m, 1 H), 7.26 (t, 1 H), 6.45 (br. s., 2 H), 2.16 (s, 3 H), 1.50 (m, 1 H), 0.33 (m, 2 H), 0.22 (m, 1 H), 0.02 (m, 1 H); MS (ES) *m/z* 335 $[M+1]^+$.

Example 28

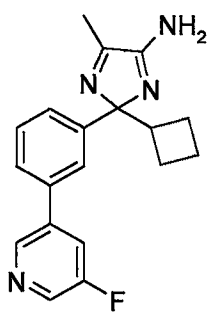
2-(3-(5-Chloropyridin-3-yl)phenyl)-2-cyclobutyl-5-methyl-2H-imidazol-4-amine



The title compound was synthesized as described for Example 14 in 29% yield starting from 5-chloropyridin-3-ylboronic acid (43.4 mg, 0.28 mmol) and 2-(3-bromophenyl)-2-cyclobutyl-5-methyl-2H-imidazol-4-amine (65 mg, 0.21 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.77 (d, 1 H), 8.63 (d, 1 H), 8.14 (t, 1 H), 7.86 (t, 1 H), 7.62 (m, 2 H), 7.41 (t, 1 H), 6.50 (br. s., 2 H), 3.05 (m, 1 H), 2.19 (s, 3 H), 1.74 (m, 1 H), 1.59 (m, 5 H); MS (ES) *m/z* 339 $[M+1]^+$.

Example 29

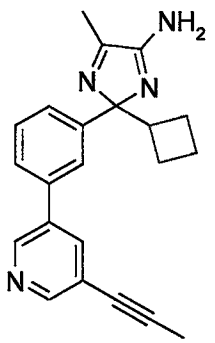
2-Cyclobutyl-2-(3-(5-fluoropyridin-3-yl)phenyl)-5-methyl-2H-imidazol-4-amine



The title compound was synthesized as described for Example 14 in 48% yield starting from 5-fluoropyridin-3-ylboronic acid (38.9 mg, 0.28 mmol) and 2-(3-bromophenyl)-2-cyclobutyl-5-methyl-2H-imidazol-4-amine (65 mg, 0.21 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.70 (t, 1 H), 8.58 (d, 1 H), 7.96 (m, 1 H), 7.86 (t, 1 H), 7.61 (m, 2 H), 7.41 (t, 1 H), 6.50 (br. s., 2 H), 3.05 (m, 1 H), 2.19 (m, 3 H), 1.73 (m, 1 H), 1.60 (m, 5 H); MS (ES) *m/z* 323 $[M+1]^+$.

Example 30

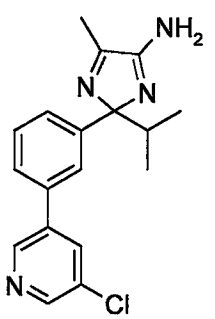
2-Cyclobutyl-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-4-amine



The title compound was synthesized as described for Example 14 in 25% yield starting from 5-(prop-1-ynyl)pyridin-3-ylboronic acid (51.3 mg, 0.32 mmol) and 2-(3-bromophenyl)-2-cyclobutyl-5-methyl-2H-imidazol-4-amine (65 mg, 0.21 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.74 (d, 1 H), 8.57 (d, 1 H), 7.97 (t, 1 H), 7.83 (t, 1 H), 7.60 (m, 2 H), 7.40 (t, 1 H), 6.49 (br. s., 2 H), 3.04 (m, 1 H), 2.19 (s, 3 H), 2.12 (s, 3 H), 1.73 (m, 1 H), 1.58 (m, 5 H); MS (ES) *m/z* 343 $[M+1]^+$.

Example 31

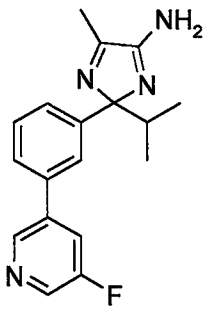
2-(3-(5-Chloropyridin-3-yl)phenyl)-2-isopropyl-5-methyl-2H-imidazol-4-amine



The title compound was synthesized as described for Example 14 in 30% yield starting from 5-chloropyridin-3-ylboronic acid (45.2 mg, 0.29 mmol) and 2-(3-bromophenyl)-2-isopropyl-5-methyl-2H-imidazol-4-amine (65mg, 0.22 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.78 (d, 1 H), 8.62 (d, 1 H), 8.14 (t, 1 H), 7.85 (t, 1 H), 7.62 (m, 2 H), 7.42 (t, 1 H), 6.46 (br. s., 2 H), 2.26 (quin, 1 H), 2.17 (s, 3 H), 0.76 (d, 3 H), 0.65 (d, 3 H); MS (ES) *m/z* 327 $[M+1]^+$.

Example 32

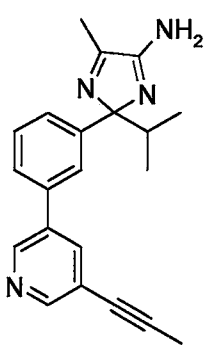
2-(3-(5-Fluoropyridin-3-yl)phenyl)-2-isopropyl-5-methyl-2H-imidazol-4-amine



The title compound was synthesized as described for Example 14 in 40% yield starting from 5-fluoropyridin-3-ylboronic acid (40.5 mg, 0.29 mmol) and 2-(3-bromophenyl)-2-isopropyl-5-methyl-2H-imidazol-4-amine (65mg, 0.22 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.68 - 8.74 (m, 1 H) 8.58 (d, 1 H) 7.94 - 8.01 (m, 1 H) 7.84 - 7.90 (m, 1 H) 7.59 - 7.66 (m, 2 H) 7.42 (t, 1 H) 6.46 (br. s., 2 H) 2.26 (quintet, 1 H) 2.17 (s, 3 H) 0.76 (d, 3 H) 0.65 (d, 3 H); MS (ES) *m/z* 311 $[M+1]^+$.

Example 33

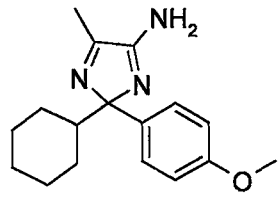
2-Isopropyl-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-4-amine



The title compound was synthesized as described for Example 14 in 34% yield starting from 5-(prop-1-ynyl)pyridin-3-ylboronic acid (53.3 mg, 0.33 mmol) and 2-(3-bromophenyl)-2-isopropyl-5-methyl-2H-imidazol-4-amine (65mg, 0.22 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.75 (d, 1 H) 8.57 (d, 1 H) 7.97 (t, 1 H) 7.80 - 7.84 (m, 1 H) 7.56 - 7.63 (m, 2 H) 7.40 (t, 1 H) 6.46 (br. s., 2 H) 2.24 (quintet, 1 H) 2.17 (s, 3 H) 2.11 (s, 3 H) 0.76 (d, 3 H) 0.65 (d, 3 H); MS (ES) *m/z* 331 $[M+1]^+$.

Example 34

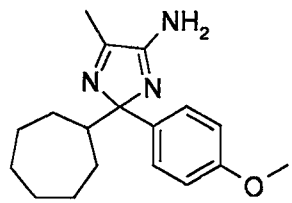
2-Cyclohexyl-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine



The title compound was synthesized as described for Example 13 in 40% yield starting from 2-cyclohexyl-2-(4-methoxyphenyl)-4-methyl-1H-imidazole-5(2H)-thione (0.55 g, 1.82 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.38 - 7.45 (m, 2 H) 6.76 - 6.83 (m, 2 H) 6.33 (br. s., 2 H) 3.70 (s, 3 H) 2.13 (s, 3 H) 1.63 - 1.73 (m, 1 H) 1.45 - 1.61 (m, 4 H) 1.33 - 1.42 (m, 1 H) 0.86 - 1.09 (m, 4 H) 0.69 - 0.81 (m, 1 H); MS (ES) *m/z* 286 $[M+1]^+$.

Example 35

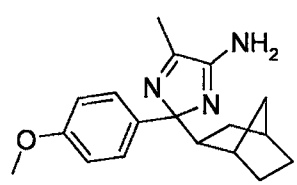
2-Cycloheptyl-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine



The title compound was synthesized as described for Example 13 in 29% yield starting from 2-cycloheptyl-2-(4-methoxyphenyl)-4-methyl-1H-imidazole-5(2H)-thione (0.42 g, 1.33 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.37 - 7.43 (m, 2 H) 6.76 - 6.82 (m, 2 H) 3.70 (s, 3 H) 2.13 (s, 3 H) 1.91 - 1.98 (m, 1 H) 1.30 - 1.54 (m, 8 H) 1.12 - 1.27 (m, 2 H) 1.01 - 1.11 (m, 1 H) 0.86 - 0.97 (m, 1 H); MS (ES) *m/z* 300 $[M+1]^+$.

Example 36

2-(Bicyclo[2.2.1]heptan-2-yl)-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine

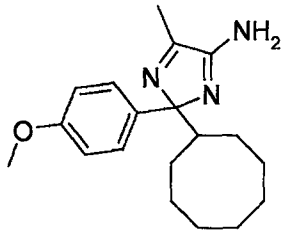


The title compound was synthesized as described for Example 13 in 17% yield starting from 2-(bicyclo[2.2.1]heptan-2-yl)-2-(4-methoxyphenyl)-4-methyl-1H-imidazole-5(2H)-

thione (120mg, 0.38 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.41 - 7.48 (m, 2 H) 6.77 - 6.83 (m, 2 H) 6.21 - 6.37 (m, 2 H) 3.69 - 3.71 (m, 3 H) 2.10 - 2.17 (m, 3 H) 1.97 - 2.04 (m, 2 H) 1.67 - 1.72 (m, 1 H) 1.24 - 1.41 (m, 3 H) 1.03 - 1.11 (m, 1 H) 0.87 - 1.03 (m, 3 H) 0.71 - 0.83 (m, 1 H); MS (ES) *m/z* 298 $[M+1]^+$.

Example 37

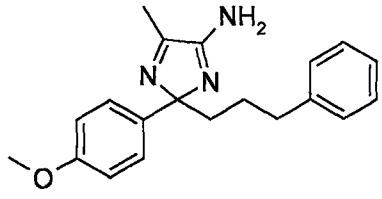
2-Cyclooctyl-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine



The title compound was synthesized as described for Example 13 in 5% yield starting from 2-cyclooctyl-2-(4-methoxyphenyl)-4-methyl-1H-imidazole-5(2H)-thione (43mg, 0.13 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.38 - 7.42 (m, 2 H) 6.77 - 6.82 (m, 2 H) 6.32 (br. s., 2 H) 3.70 (s, 3 H) 2.12 (s, 3 H) 1.32 - 1.55 (m, 10 H) 1.16 - 1.26 (m, 2 H) 1.03 - 1.16 (m, 2 H) 0.89 - 1.00 (m, 1 H); MS (ES) *m/z* 314 $[M+1]^+$.

Example 38

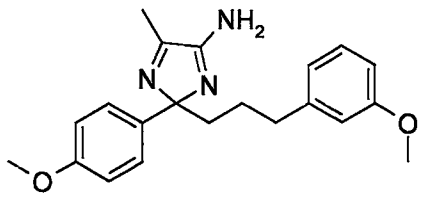
2-(4-Methoxyphenyl)-5-methyl-2-(3-phenylpropyl)-2H-imidazol-4-amine



The title compound was synthesized as described for Example 13 in 41% yield starting from 2-(4-methoxyphenyl)-4-methyl-2-(3-phenylpropyl)-1H-imidazole-5(2H)-thione (0.42g, 1.24 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.38 - 7.44 (m, 2 H) 7.22 (m, 2 H) 7.12 (m, 1 H) 7.06 (d, 2 H) 6.77 - 6.83 (m, 2 H) 6.34 (br. s., 2 H) 3.70 (s, 3 H) 2.43 (t, 2 H) 2.12 (s, 3 H) 1.83 (m, 1 H) 1.60 - 1.68 (m, 1 H) 1.24 - 1.36 (m, 2 H); MS (ES) *m/z* 322 $[M+1]^+$.

Example 39

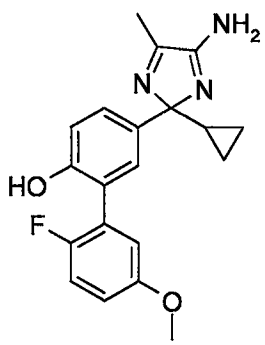
2-(4-Methoxyphenyl)-2-(3-(3-methoxyphenyl)propyl)-5-methyl-2H-imidazol-4-amine



The title compound was synthesized as described for Example 13 in 47% yield starting from 2-(4-methoxyphenyl)-2-(3-(3-methoxyphenyl)propyl)-4-methyl-1H-imidazole-5(2H)-thione (0.27 g, 0.73 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.38 - 7.44 (m, 2 H) 7.13 (t, 1 H) 6.77 - 6.84 (m, 2 H) 6.69 (m, 1 H) 6.60 - 6.66 (m, 2 H) 6.34 (br. s., 2 H) 3.70 (s, 3 H) 3.69 (s, 3 H) 2.41 (t, 2 H) 2.13 (s, 3 H) 1.83 (ddd, 1 H) 1.60 - 1.68 (m, 1 H) 1.23 - 1.35 (m, 2 H); MS (ES) *m/z* 352 $[M+1]^+$.

Example 40

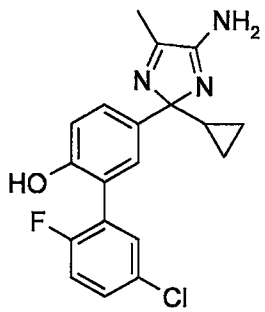
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2'-fluoro-5'-methoxybiphenyl-2-ol



The title compound was synthesized as described for Example 14 in 30% yield starting from 4-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-bromophenol (60mg, 0.19 mmol) and 2-fluoro-5-methoxyphenylboronic acid (39.7 mg, 0.23 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.42 (br. s., 1 H) 7.36 - 7.41 (m, 1 H) 7.30 - 7.34 (m, 1 H) 7.13 (t, 1 H) 6.87 - 6.92 (m, 1 H) 6.80 - 6.85 (m, 2 H) 6.37 (br. s., 2 H) 3.75 (s, 3 H) 2.12 (s, 3 H) 1.40 - 1.47 (m, 1 H) 0.24 - 0.32 (m, 2 H) 0.14 - 0.22 (m, 1 H) -0.08 - -0.01 (m, 1 H); MS (ES) *m/z* 354 $[M+1]^+$.

Example 41

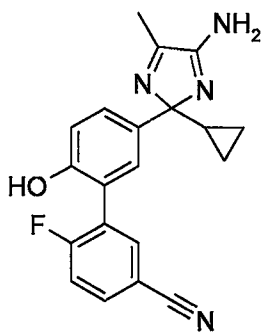
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-5'-chloro-2'-fluorobiphenyl-2-ol



The title compound was synthesized as described for Example 14 in 34% yield starting from 4-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-bromophenol (60mg, 0.19 mmol) and 5-chloro-2-fluorophenylboronic acid (40.7 mg, 0.23 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.57 (s, 1 H) 7.40 - 7.46 (m, 2 H) 7.35 - 7.39 (m, 1 H) 7.32 - 7.35 (m, 1 H) 7.29 (t, 1 H) 6.85 (d, 1 H) 6.39 (br. s., 2 H) 2.13 (s, 3 H) 1.40 - 1.48 (m, 1 H) 0.24 - 0.32 (m, 2 H) 0.14 - 0.22 (m, 1 H) -0.08 - 0.00 (m, 1 H); MS (ES) *m/z* 358 $[M+1]^+$.

Example 42

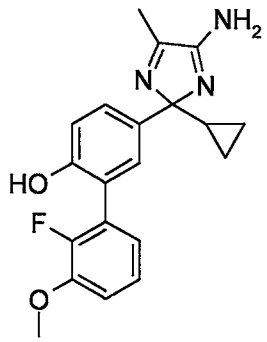
5'-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-6-fluoro-2'-hydroxybiphenyl-3-carbonitrile



The title compound was synthesized as described for Example 14 in 11% yield starting from 4-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-bromophenol (60mg, 0.19 mmol) and 5-cyano-2-fluorophenylboronic acid (38.5 mg, 0.23 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.67 (br. s., 1 H) 7.85 - 7.93 (m, 2 H) 7.43 - 7.51 (m, 2 H) 7.34 - 7.37 (m, 1 H) 6.87 (d, 1 H) 6.39 (br. s., 2 H) 2.13 (s, 3 H) 1.40 - 1.49 (m, 1 H) 0.25 - 0.32 (m, 2 H) 0.15 - 0.22 (m, 1 H) -0.07 - 0.01 (m, 1 H); MS (ES) *m/z* 349 $[M+1]^+$.

Example 43

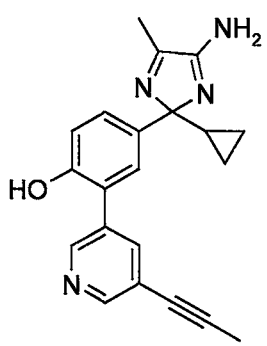
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2'-fluoro-3'-methoxybiphenyl-2-ol



The title compound was synthesized as described for Example 14 in 25% yield starting from 4-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-bromophenol (60mg, 0.19 mmol) and 2-fluoro-3-methoxyphenylboronic acid (39.7 mg, 0.23 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.38 (s, 1 H) 7.37 - 7.41 (m, 1 H) 7.29 (d, 1 H) 7.09 - 7.16 (m, 2 H) 6.79 - 6.86 (m, 2 H) 6.37 (br. s., 2 H) 3.85 (s, 3 H) 2.12 (s, 3 H) 1.38 - 1.46 (m, 1 H) 0.23 - 0.31 (m, 2 H) 0.14 - 0.22 (m, 1 H) -0.08 - 0.00 (m, 1 H); MS (ES) *m/z* 354 $[M+1]^+$.

Example 44

4-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(5-(prop-1-ynyl)pyridin-3-yl)phenol

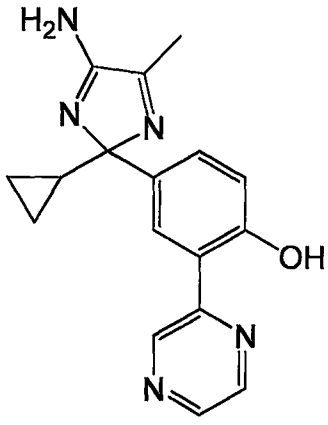


The title compound was synthesized as described for Example 14 in 28% yield starting from 4-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-bromophenol (60mg, 0.19 mmol) and 5-(prop-1-ynyl)pyridin-3-ylboronic acid (47.0 mg, 0.29 mmol): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.72 (br. s., 1 H) 8.61 (d, 1 H) 8.50 (d, 1 H) 7.85 (t, 1 H) 7.44 - 7.49 (m, 1 H) 7.38 - 7.44 (m, 1 H) 6.88 (d, 1 H) 6.41 (br. s., 2 H) 2.13 (s, 3 H) 2.10 (s, 3 H)

1.44 - 1.52 (m, 1 H) 0.24 - 0.33 (m, 2 H) 0.14 - 0.23 (m, 1 H) -0.07 - 0.03 (m, 1 H); MS (ES) *m/z* 345 $[M+1]^+$.

Example 45

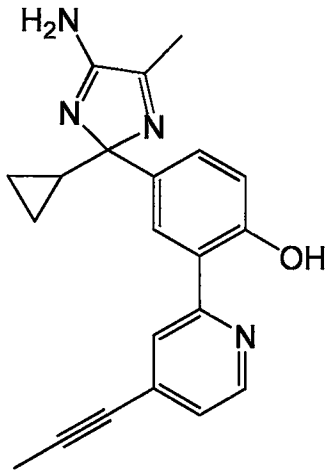
4-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(pyrazin-2-yl)phenol



2-Cyclopropyl-2-(4-methoxy-3-(pyrazin-2-yl)phenyl)-5-methyl-2H-imidazol-4-amine (0.08 g, 0.25 mmol) was dissolved in dichloromethane (3.00 mL) and boron tribromide (0.165 mL, 1.74 mmol) was added. The mixture was stirred at room temperature for 30 min. The reaction was quenched by dropwise addition of MeOH (2 mL). NH_4OH (28-30 wt% NH_3 in water, 1 mL) was added. The resulting mixture was stirred for 5 min, then concentrated HCl was added dropwise until ~pH 7. Additional dichloromethane was added and the organic layer was collected. The water phase was extracted with dichloromethane. NaCl was added and the water phase was extracted with acetonitrile (three times). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was redissolved in dichloromethane and concentrated *in vacuo*. The produc twas purified by silica chromatography using 0% to 10% (3.5 M ammonia in methanol) in dichloromethane to give 4-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(pyrazin-2-yl)phenol (0.036 g, 47% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.89 (br. s., 1 H), 9.26 (d, 1 H), 8.70 (dd, 1 H), 8.55 (d, 1 H), 8.08 (d, 1 H), 7.51 (dd, 1 H), 6.91 (d, 1 H), 6.43 (br. s., 2 H), 2.14 (s, 3 H), 1.42 - 1.54 (m, 1 H), 0.24 - 0.36 (m, 2 H), 0.14 - 0.24 (m, 1 H), -0.06 - 0.04 (m, 1 H); MS (ES+) *m/z* 308 $[M+H]^+$.

Example 46

4-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(4-(prop-1-ynyl)pyridin-2-yl)phenol

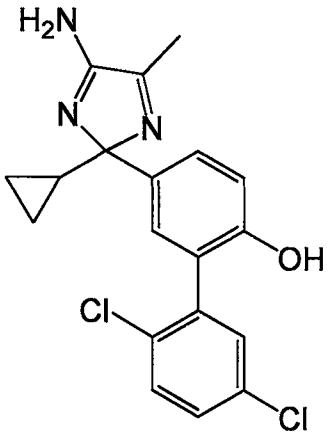


2-Cyclopropyl-2-(4-methoxy-3-(4-(prop-1-ynyl)pyridin-2-yl)phenyl)-5-methyl-2H-imidazol-4-amine (0.016 g, 0.04 mmol) was dissolved in dichloromethane (1.00 mL) and cooled to -78 °C. Boron tribromide (0.015 mL, 0.16 mmol) was dropwise added. The reaction mixture was slowly warmed to room temperature over night. The reaction was quenched by dropwise addition of MeOH (0.5 mL). NH_4OH (28-30 wt% NH_3 in water) (0.5 mL) was added and the mixture was stirred for 5 min. HCl was added dropwise until ~pH 7. The organic solvents were removed *in vacuo*. Dichloromethane was added and the organic layer was collected. The water phase was extracted with dichloromethane (three times). NaCl was added and the water phase was extracted with ethyl acetate (three times). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*.

The product was purified by prep-HPLC to give 4-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(4-(prop-1-ynyl)pyridin-2-yl)phenol (2.1 mg, 14% yield) : ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 13.21 (br. s, 1 H), 8.58 (d, 1 H), 8.07 (d, 1 H), 7.94 (s, 1 H), 7.50 (dd, 1 H), 7.37 (dd, 1 H), 6.85 (d, 1 H), 6.45 (br. s, 2 H), 2.16 (d, 6 H), 1.53 (tt, 1 H), 0.25 - 0.34 (m, 2 H), 0.16 - 0.23 (m, 1 H), -0.03 - 0.04 (m, 1 H); MS (ES-) *m/z* 343 $[M-H]^-$; MS (ES+) *m/z* 345 $[M+H]^+$.

Example 47

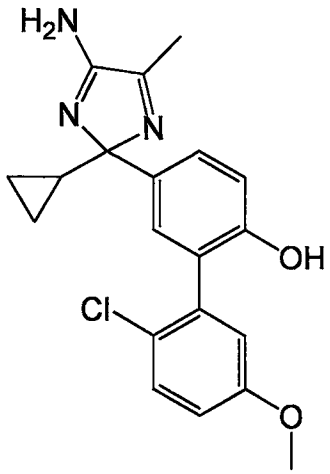
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2',5'-dichlorobiphenyl-2-ol



2-Cyclopropyl-2-(2',5'-dichloro-6-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-4-amine (60.2 mg, 0.16 mmol) was dissolved in dichloromethane (3.00 mL) and boron tribromide (0.103 mL, 1.09 mmol) was added. The reaction mixture was stirred at room temperature over night. The reaction was quenched by dropwise addition of MeOH (2 mL). NH_4OH (28-30 wt% NH_3 in water, 1 mL) was added And the mixture was stirred for 5 min. HCl was added dropwise until ~pH 7. Additional dichloromethane was added and the organic layer was collected. The water phase was extracted with dichloromethane (twice). The combined organic layers were passed through a phase separator and concentrated *in vacuo*. The product was purified by preparative HPLC. The desired fractions were pooled and concentrated *in vacuo*. The residue was redissolved in acetonitrile and methanol and water was added and the product was freeze-dried over night. The residue was partitioned between water (pH ~7) and dichloromethane (x5), the combined organic layers were passed through a phase separator and concentrated *in vacuo* to give 5-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2',5'-dichlorobiphenyl-2-ol (7.60 mg, 13% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.53 (br. s., 1 H), 7.54 (d, 1 H), 7.42 (td, 2 H), 7.34 (d, 1 H), 7.25 (d, 1 H), 6.85 (d, 1 H), 6.38 (br. s., 2 H), 2.15 (br. s., 3 H), 1.44 (br. s., 1 H), 0.12 - 0.43 (m, 3 H), 0.00 (br. s., 1 H); MS (ES+) *m/z* 374 $[M+H]^+$; MS (ES-) *m/z* 372 $[M-H]^-$.

Example 48

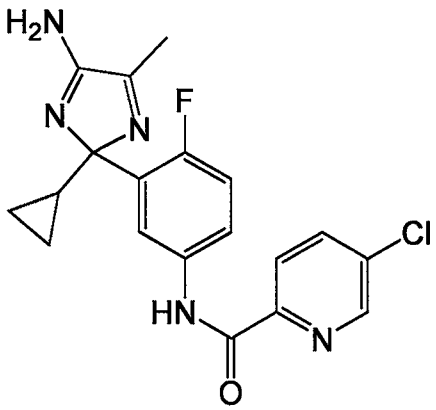
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2'-chloro-5'-methoxybiphenyl-2-ol



2-Chloro-5-methoxyphenylboronic acid (93 mg, 0.50 mmol), 4-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-bromophenol (153.5 mg, 0.50 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride (20.49 mg, 0.02 mmol), cesium carbonate (487 mg, 1.49 mmol) and DME:EtOH:Water 6:3:1 (4.00 mL) were put in a microwave vial and irradiated in a microwave reactor at 150 °C for 30 min, and then concentrated *in vacuo*. Dichloromethane and methanol were added to the residue and the resulting mixture was filtered through a syringe filter. The filtrate was concentrated *in vacuo* And the residue purified by silica chromatography using 0% to 10% (3.5 M ammonia in methanol) in dichloromethane. The desired fractions were pooled and concentrated *in vacuo* and purified by preparative HPLCto give 5-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2'-chloro-5'-methoxybiphenyl-2-ol (9.80 mg, 5% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.36 (br. s., 1 H), 7.34 - 7.41 (m, 2 H), 7.24 (d, 1 H), 6.92 (dd, 1 H), 6.80 (dd, 2 H), 6.36 (br. s., 2 H), 3.75 (s, 3 H), 2.12 (s, 3 H), 1.37 - 1.45 (m, 1 H), 0.24 - 0.33 (m, 2 H), 0.14 - 0.22 (m, 1 H), -0.07 - 0.00 (m, 1 H); MS (ES-) *m/z* 368 $[M-H]^-$; MS (ES+) *m/z* 370 $[M+H]^+$.

Example 49

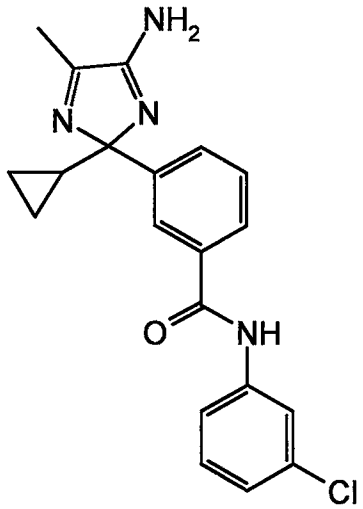
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-4-fluorophenyl)-5-chloropicolinamide



5-Chloro-2-pyridinecarboxylic acid (28.0 mg, 0.18 mmol), 2-(5-amino-2-fluorophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (43.7 mg, 0.18 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (34.0 mg, 0.18 mmol) were dissolved in DMF and hydrochloric acid (2 M, 0.089 mL, 0.18 mmol) was added. The mixture was stirred at room temperature for 3 days, then quenched by addition of aqueous $KHSO_4$ (1 M). The aqueous phase was extracted with ethyl acetate (three times). The water mixture was poured onto a hydromatrix column and eluted with ethyl acetate, then acetonitrile. The pH of the water phase was adjusted to ~8 with aqueous NaOH (5 M) and it was extracted with ethyl acetate. The combined organic layers were passed through a phase separator and then concentrated *in vacuo*. The product was purified by preparative HPLC. The desired fractions were pooled and concentrated *in vacuo*. The residue was partitioned between water (pH approximately 8) and dichloromethane (twice). Tthe combined organic layers were passed through a phase separator and concentrated *in vacuo* to give N-(3-(4-amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-4-fluorophenyl)-5-chloropicolinamide (5.00 mg, 7% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.64 (s, 1 H), 8.77 (d, 1 H), 8.17 - 8.23 (m, 1 H), 8.12 - 8.17 (m, 1 H), 8.09 (dd, 1 H), 7.73 (dt, 1 H), 7.08 (dd, 1 H), 6.54 (br. s., 2 H), 2.16 (s, 3 H), 1.75 - 1.82 (m, 1 H), 0.30 - 0.41 (m, 2 H), 0.17 - 0.26 (m, 1 H), -0.08 - 0.00 (m, 1 H); MS (ES-) *m/z* 384 $[M-H]^-$; MS (ES+) *m/z* 386 $[M+H]^+$.

Example 50

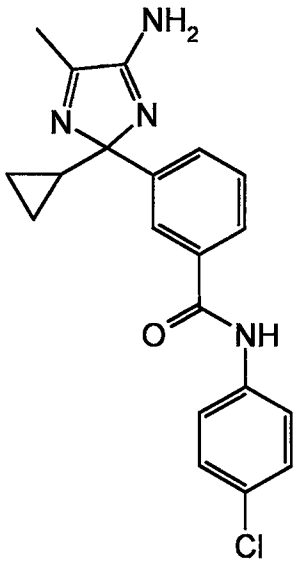
3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-N-(3-chlorophenyl)benzamide



Palladium(II) acetate (7.68 mg, 0.03 mmol) and 1,3-bis(diphenylphosphino)propane (14.12 mg, 0.03 mmol) were added to a high pressure reactor (200 mL), then 2-(3-bromophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (100 mg, 0.34 mmol) in dioxane (5 mL) was added, followed by 3-chloroaniline (0.362 mL, 3.42 mmol) and TEA (0.143 mL, 1.03 mmol). The reactor was connected to a carbon monoxide source, a nitrogen (g) source and a vacuum line. The mixture, under an atmosphere of N_2 (g), was evacuated 3 times, then the procedure was repeated with carbon monoxide (excess) 3 times. The pressure was adjusted to 4 bar of CO (g) and then the reactor was placed in an oil-bath set to 90 °C. After 90 h, the reaction vessel was allowed to cool and removed from the carbon monoxide source. The reaction mixture was diluted with MeOH/DCM and filtered through Celite, then concentrated.. The product was purified by preparative chromatography to give the title compound in 37 mg (30 % yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm -0.03 - 0.08 (m, 1 H) 0.18 - 0.27 (m, 1 H) 0.27 - 0.38 (m, 2 H) 1.48 - 1.60 (m, 1 H) 2.17 (s, 3 H) 6.48 - 6.55 (m, 2 H) 7.13 - 7.19 (m, 1 H) 7.33 - 7.42 (m, 1 H) 7.42 - 7.47 (m, 1 H) 7.66 - 7.74 (m, 1 H) 7.75 - 7.85 (m, 2 H) 7.91 - 7.99 (m, 1 H) 8.08 - 8.17 (m, 1 H) 10.37 - 10.45 (m, 1 H) ; MS (APCI$^+$) m/z 367 $(M+H)^+$.

Example 51

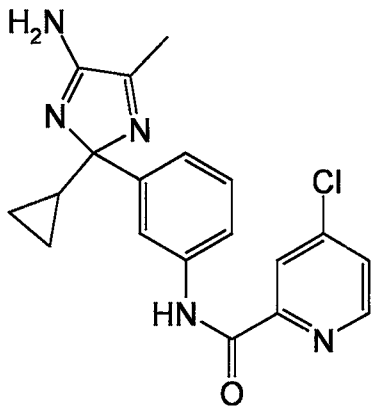
3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-N-(4-chlorophenyl)benzamide



Palladium(II) acetate (7.68 mg, 0.03 mmol) and 1,3-bis(diphenylphosphino)propane (14.12 mg, 0.03 mmol) were added to a high pressure reactor (200 mL), then 2-(3-bromophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (100 mg, 0.34 mmol) was added, followed by 4-chloroaniline (437 mg, 3.42 mmol), toluene (5 mL) and TEA (0.143 mL, 1.03 mmol). The reactor was connected to a carbon monoxide source, a nitrogen (g) source and a vacuum line. The mixture, under an atmosphere of N_2 (g), was evacuated 3 times, then the procedure was repeated with carbon monoxide (excess) 3 times. The pressure was adjusted to 4 bar of CO (g) and then the reactor was placed in an oil-bath set to 90 °C. After 71 h, the reaction vessel was allowed to cool and removed from the carbon monoxide source. The reaction mixture was diluted with MeOH/DCM and filtered through Celite, then concentrated. The product was purified by preparative chromatography to give the title compound in 37mg (30% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm -0.02 - 0.08 (m, 1 H) 0.18 - 0.28 (m, 1 H) 0.29 - 0.39 (m, 2 H) 1.51 - 1.60 (m, 1 H) 2.18 (br. s., 3 H) 6.44 - 6.58 (m, 2 H) 7.38 - 7.43 (m, 2 H) 7.43 - 7.47 (m, 1 H) 7.76 - 7.83 (m, 4 H) 8.10 (s, 1 H) 10.37 (s, 1 H); MS (APCI$^+$) m/z 367 $(M+H)^+$.

Example 52

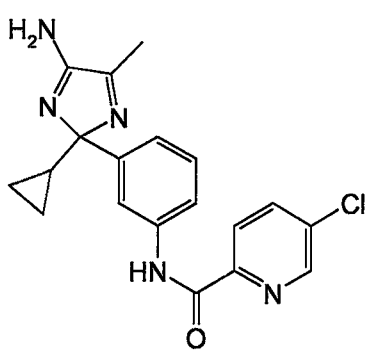
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)phenyl)-4-chloropicolinamide



4-Chloropicolinic acid (106 mg, 0.67 mmol) and 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (129 mg, 0.67 mmol) was stirred in N,N-dimethylformamide (2 mL) at rt for 15 minutes. The solution was cooled to 0 °C (external temperature) in an ice-water bath and a solution of 2-(3-aminophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (128 mg, 0.56 mmol) and aqueous hydrochloric acid (3 M) (0.187 mL, 0.56 mmol) in N,N-dimethylformamide (2.000 mL) was added dropwise over 5 minutes. The reaction was stirred at 0 °C for 5 minutes and then at ambient temperature for 3 hours. MeOH (1 mL) was added to quench the reaction and the reaction was stirred over night. The mixture was purified by preparative HPLC to yield the title compound (24 mg, 12 % yield, containing 10% MeOH): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.60 (s, 1 H) 8.72 (d, 1 H) 8.15 (d, 1 H) 8.12 (t, 1 H) 7.84 (dd, 1 H) 7.68 (m, 1 H) 7.34 (dt, 1 H) 7.25 (t, 1 H) 6.45 (s, 2 H) 4.10 (q, 0.1 H, MeOH) 3.17 (d, 0.3 H, MeOH) 2.16 (s, 3 H) 1.50 (m, 1 H) 0.32 (m, 2 H) 0.2 (m, 1 H) 0.00 (m, 1 H); MS (ES+) m/z 368 $[M+H]^+$.

Example 53

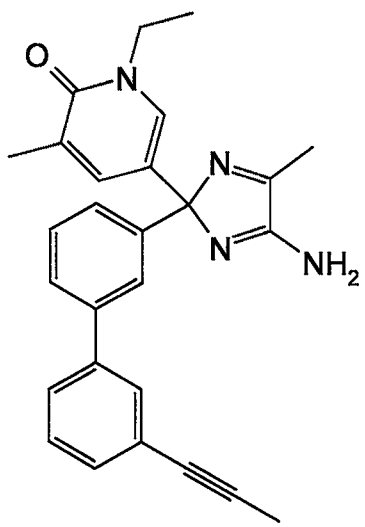
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)phenyl)-5-chloropicolinamide



The title compound was synthesized as described for Example 52 starting from 5-chloro-2-pyridinecarboxylic acid (69.0 mg, 0.44 mmol) and 2-(3-aminophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine (100 mg, 0.44 mmol), with the exception that the reaction time was 140 minutes, to give the title compound (22 mg, 14% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.55 (s, 1 H) 8.78 (m, 1 H) 8.20 (dd, 1 H) 8.15 (d, 1 H) 8.11 (t, 1 H) 7.68 (m, 1 H) 7.33 (dt, 1 H) 7.25 (t, 1 H) 6.44 (s, 2 H) 2.16 (s, 3 H) 1.50 (m, 1 H) 0.32 (m, 2 H) 0.21 (m, 1 H) 0.00 (m, 1 H); MS (ES+) m/z 368 $[M+H]^+$.

Example 54

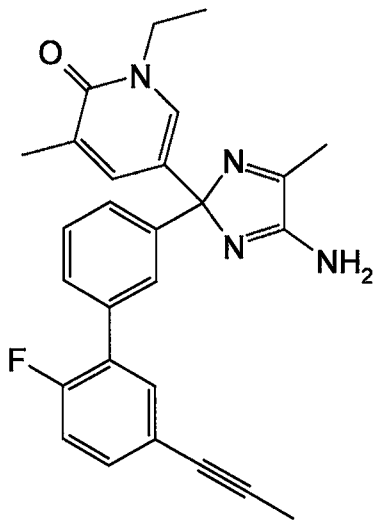
5-(4-Amino-5-methyl-2-(3'-(prop-1-ynyl)biphenyl-3-yl)-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one



The title compound was synthesized as described for Example 17 starting from 5-(4-amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one (71.0 mg, 0.18 mmol) and 3-(prop-1-ynyl)phenylboronic acid (88 mg, 0.55 mmol), with the following exceptions: The reaction time was 20 minutes and the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and DCM before purification. The DCM layer was passed through a phase separator and concentrated before the purification. Preparative HPLC gave 15 mg (19% yield) of the title compound: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.73 (t, 1 H) 7.52 - 7.57 (m, 4 H) 7.50 (m, 1 H) 7.40 - 7.46 (m, 2 H) 7.32 - 7.40 (m, 2 H) 6.68 (s, 2 H) 3.88 (q, 2 H) 2.24 (s, 3 H) 2.07 (s, 3 H) 1.93 (s, 3 H) 1.16 (t, 3 H); MS (ES+) m/z 423 $[M+H]^+$.

Example 55

5-(4-Amino-2-(2'-fluoro-5'-(prop-1-ynyl)biphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one



The title compound was synthesized as described for Example 17 starting from 5-(4-amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one (71.0 mg, 0.18 mmol) and 3-(prop-1-ynyl)phenylboronic acid (88 mg, 0.55 mmol), with the exception that it was purified twice by preparative HPLC to give the title compound, 27 mg (31% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.64 (s, 1 H) 7.53 - 7.57 (m, 1 H) 7.52 (d, 1 H) 7.37 - 7.46 (m, 5 H) 7.29 (dd, 1 H) 6.68 (br. s., 2 H) 3.88 (q, 2 H) 2.24 (s, 3 H) 2.05 (s, 3 H) 1.93 (s, 3 H) 1.16 (t, 3 H); MS (ES+) m/z 441 $[M+H]^+$

The level of activity of the compounds was tested using the following methods:

TR-FRET Assay

The β–secretase enzyme used in the TR-FRET is prepared as follows:
The cDNA for the soluble part of the human β-Secretase (AA 1 – AA 460) was cloned using the ASP2-Fc10-1-IRES-GFP-neoK mammalian expression vector. The gene was fused to the Fc domain of IgG1 (affinity tag) and stably cloned into HEK 293 cells. Purified sBACE-Fc was stored in –80 °C in Tris buffer, pH 9.2 and had a purity of 95%.

The enzyme (truncated form) was diluted to 6 µg/mL (stock 1.3 mg/mL) and the substrate (Europium)CEVNLDAEFK(Qsy7) to 200 nM (stock 120 µM) in reaction buffer (NaAcetate, chaps, triton x-100, EDTA pH4.5). The robotic systems Biomek FX and Velocity 11 were used for all liquid handling and the enzyme and substrate solutions were kept on ice until they were placed in the robotic system. Enzyme (9 µl) was added to the plate then 1 µl of compound in dimethylsulphoxide was added, mixed and pre-incubated for 10 minutes. Substrate (10 µl) was then added, mixed and the reaction proceeded for 15 minutes at room temperature. The reaction was stopped with the addition of Stop solution (7 µl, NaAcetate, pH 9). The fluorescence of the product was measured on a Victor II plate reader with an excitation wavelength of 340nm and an emission wavelength of 615nm. The assay was performed in a Costar 384 well round bottom, low volume, non-binding surface plate (Corning #3676). The final concentration of the enzyme was 2.7 µg/ml; the final concentration of substrate was 100 nM (Km of ~250 nM). The dimethylsulphoxide control, instead of test compound, defined the 100% activity level and 0% activity was defined by wells lacking enzyme (replaced with reaction buffer). A control inhibitor was also used in dose response assays and had an IC50 of ~575 nM.

sAPPβ release assay

SH-SY5Y cells were cultured in DMEM /F-12 with Glutamax, 10% FCS and 1% non-essential aminoacids and cryopreserved and stored at -140°C at a concentration of 7.5x106 cells per vial. Thaw cells and seed at a conc. of 1.5x105/ml in DMEM /F-12 with

Glutamax, 10% FCS and 1% non-essential aminoacids to a 96-well tissue culture treated plate, 100µl cell susp/well. The cell plates were then incubated for 7 hours at 37 °C, 5% CO2. The cell medium was removed, followed by addition of 90 µl compound diluted in DMEM /F-12 with Glutamax, 10% FCS, 1% non-essential aminoacids and 1% PeSt to a final conc. of 1% DMSO. The compounds were incubated with the cells for 16h (over night) at 37 °C, 5% CO2. Meso Scale Discovery (MSD) plates were used for the detection of sAPPβ release. MSD sAPPβ plates were blocked in 3% BSA in Tris wash buffer (150µl/well) for 1 hour in RT and washed 4 times in Tris wash buffer (150µl/well). 50 µl of medium was transferred to the pre-blocked and washed MSD sAPPβ microplates, and the cell plates were further used in an ATP assay to measure cytotoxicity. The MSD plates were incubated with shaking in RT for 1 hour followed by washing 4 times. 25 µl detection antibody was added (1nM) per well followed by incubation with shaking in RT for 1h and washing 4 times. 150 µl Read Buffer was added per well and the plates were read in a SECTOR Imager.

ATP assay

As indicated in the sAPPβ release assay, after transferring 50 µL medium from the cell plates for sAPPβ detection, the plates were used to analyse cytotoxicity using the ViaLightTM Plus cell proliferation/cytotoxicity kit from Cambrex BioScience that measures total cellular ATP. The assay was performed according to the manufacture's protocol. Briefly, 25µL cell lysis reagent was added per well. The plates were incubated at room temperature for 10 min. Two min after addition of 50 µL reconstituted ViaLightTM Plus ATP reagent, the luminescence was measured in a Wallac Victor2 1420 multilabel counter.

Results

Typical IC50 values for the compounds of the present invention are in the range of about 1 to about 100,000 nM. Biological data is given below in Table I

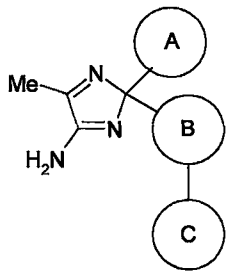
Table I.

Example No.	**IC50 in TR-FRET assay (nM)**		**Example No.**	**IC50 in TR-FRET assay (nM)**
1	3519		30	134
2	1824		31	2055
3	12884		32	8161
4	12538		33	421
5	1127		34	7521
6	1426		35	8311
7	3039		36	1043
8	795		37	1281
9	-		38	21990
10	2562		39	5055
11a Isomer 1	-		40	765
11b Isomer 2	6623		41	827
12a Isomer 1	8099		42	1380
12b Isomer 2	-		43	1400
13	12740		44	61
14	320		45	5135
15	79		46	122
16	2820		47	102
17	37		48	1518
18	28		49	2411
19	33		50	16990
20	88		51	16900
21	336		52	21280
22	86		53	368
23	6855		54	27

24	2104		55	36
25	1627			
26	8324			
27	1112			
28	406			
29	1170			

CLAIMS

1. A compound according to formula (I):



(I)

wherein

A is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{0-6}alkylC_{3-8}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl or C_{0-6}alkyl-C_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;

B is aryl or heteroaryl; wherein said aryl or heteroaryl is optionally substituted with one or more R^2;

C is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, $NR^4(CO)N(R^4)_2$, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)N(R^4)_2$, C_{0-6}alkylSR^4, C_{0-6}alkylOSO_2R^4, C_{0-6}alkylSO_3R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, C_{0-6}alkyl$(SO_2)N(R^4)_2$, C_{0-6}alkyl$(SO)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO_2)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO)R^4$, SF_5, and OSF_5, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, C_{0-6}alkylOR^4, halogen,

C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkylCON(R^4)$_2$, O(CO)OR^4, O(CO)R^4, O(CO)N(R^4)$_2$, NR^4(CO)OR^4, C_{0-6}alkylNR^4(CO)R^4, NR^4(CO)N(R^4)$_2$, NR^4(CO)(CO)R^4, NR^4(CO)(CO)N(R^4)$_2$, C_{0-6}alkylSR^4, C_{0-6}alkylOSO$_2$R^4, C_{0-6}alkylSO$_3$R^4, C_{0-6}alkylSO$_2$R^4, C_{0-6}alkylSOR^4, C_{0-6}alkyl(SO$_2$)N(R^4)$_2$, C_{0-6}alkyl(SO)N(R^4)$_2$, C_{0-6}alkylNR^4(SO$_2$)N(R^4)$_2$, C_{0-6}alkylNR^4(SO)R^4, SF_5, and OSF_5, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl or is optionally substituted with one or more R^3; or two R^1 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^2 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylCO$_2$R^4, C_{0-6}alkylN(R^4)$_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkylCON(R^4)$_2$, O(CO)OR^4, O(CO)R^4, O(CO)N(R^4)$_2$, NR^4(CO)OR^4, C_{0-6}alkylNR^4(CO)R^4, NR^4(CO)N(R^4)$_2$, NR^4(CO)(CO)R^4, NR^4(CO)(CO)-N(R^4)$_2$, C_{0-6}alkylSR^4, C_{0-6}alkylOSO$_2$R^4, C_{0-6}alkylSO$_3$R^4, C_{0-6}alkylSO$_2$R^4, C_{0-6}alkylSOR^4, C_{0-6}alkyl(SO$_2$)N(R^4)$_2$, C_{0-6}alkyl(SO)N(R^4)$_2$, C_{0-6}alkylNR^4(SO$_2$)N(R^4)$_2$, C_{0-6}alkylNR^4(SO)-R^4 and C_{0-6}alkylOR^4, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cyclo-alkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3,
or two R^2 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^3 is selected from halogen, NO_2, CHO, C_{0-6}alkylCN, C_{0-6}alkylOR^4, C_{1-6}haloalkyl, C_{0-6}alkylN(R^4)$_2$, NR^{4}C(O)R^4, C_{0-6}alkylCO$_2$R^4, C_{0-6}alkylCON(R^4)$_2$, C_{0-6}alkylNR^4(CO)R^4, O(CO)N(R^4)$_2$, NR^4(CO)OR^4, NR^4(CO)N(R^4)$_2$, O(CO)OR^4, O(CO)R^4, C_{0-6}alkylCOR^4, NR^4(CO)(CO)R^4, NR^4(CO)(CO)N(R^4)$_2$, C_{0-6}alkylSR^4, C_{0-6}alkyl(SO$_2$)N(R^4)$_2$, OC_{2-6}alkylN-R^4(SO$_2$)R^4, C_{0-6}alkyl(SO)N(R^4)$_2$, OSO$_2$R^4, SO$_3$R^4, C_{0-6}alkylNR^4(SO$_2$)N(R^4)$_2$, C_{0-6}alkylN-R^4(SO)R^4, C_{0-6}alkylSO$_2$R^4, C_{0-6}alkylSOR^4, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkyl-C_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, and C_{0-6}alkylheterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl,

C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;

R^4 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{1-6}alkylOR^5, and C_{1-6}alkyl$N(R^5)_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^4 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^5 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheterocyclyl and C_{0-6}alkylheteroaryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkyl-C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^5 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^6 is selected from oxo, halogen, nitro, CN, OR^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylheterocyclyl, C_{1-6}haloalkyl, OC_{2-6}alkyl$N(R^7)_2$, $N(R^7)_2$, $CON(R^7)_2$, $NR^7(CO)R^7$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^7, $SON(R^7)_2$, $(SO_2)N(R^7)_2$, $NR^7SO_2R^7$, NR^7SOR^7, SO_2R^7, SOR^7, $(CO)C_{1-6}$alkyl-$N(R^7)_2$, $(SO_2)C_{1-6}$alkyl$N(R^7)_2$, OSO_2R^7 and SO_3R^7, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, or C_{0-6}alkylC_{3-6}cycloalkyl is optionally substituted with one or more substituents independently selected from halo, nitro, cyano, OR^7, C_{1-6}alkyl, or C_{1-6}haloalkyl;

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_6cycloalkynyl, aryl, heteroaryl and heterocyclyl, wherein said C_{1-}

$_{6}$alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, cyano, halogen and OC_{1-3}alkyl; or two R^7 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring being optionally substituted with one or more substituents independently selected from hydroxy, OC_{1-3}alkyl, cyano and halogen;

as a free base or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

A is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{0-6}alkylC_{3-8}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl or C_{0-6}alkyl-C_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;

B is aryl or heteroaryl; wherein said aryl or heteroaryl is optionally substituted with one or more R^2;

C is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkyl-CN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, C_{0-6}alkyl$(SO)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO_2)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO)R^4$, SF_5, and OSF_5, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, C_{0-6}alkylOR^4, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, $NR^4(CO)N(R^4)_2$, $NR^4(CO)(CO)R^4$,

$NR^4(CO)(CO)N(R^4)_2$, $C_{0-6}alkylSR^4$, $C_{0-6}alkylOSO_2R^4$, $C_{0-6}alkylSO_3R^4$, $C_{0-6}alkylSO_2R^4$, $C_{0-6}alkylSOR^4$, SF_5, and OSF_5, wherein said $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, $C_{0-6}alkylheterocyclyl$ or is optionally substituted with one or more R^3, or two R^1 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^2 is selected from $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkyl-C_{3-6}cycloalkenyl$, $C_{0-6}alkylC_6cycloalkynyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, $C_{0-6}alkyl-heterocyclyl$, $C_{0-6}alkylCO_2R^4$, $C_{0-6}alkylN(R^4)_2$, halogen, $C_{0-6}alkylCN$, $C_{0-6}alkylCOR^4$, CHO, NO_2, $C_{0-6}alkylCON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, $C_{0-6}alkylNR^4(CO)R^4$, $NR^4(CO)N(R^4)_2$, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)N(R^4)_2$, $C_{0-6}alkyl-(SO)N(R^4)_2$, $C_{0-6}alkylNR^4(SO_2)N(R^4)_2$, $C_{0-6}alkylNR^4(SO)R^4$ and $C_{0-6}alkylOR^4$, wherein said $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkyl-heteroaryl$ or $C_{0-6}alkylheterocyclyl$ is optionally substituted with one or more R^3, or two R^2 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^3 is selected from halogen, NO_2, CHO, $C_{0-6}alkylCN$, $C_{0-6}alkylOR^4$, $C_{1-6}haloalkyl$, $C_{0-6}alkylN(R^4)_2$, $NR^4C(O)R^4$, $C_{0-6}alkylCO_2R^4$, $C_{0-6}alkylCON(R^4)_2$, $C_{0-6}alkylNR^4(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, $NR^4(CO)N(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $C_{0-6}alkylCOR^4$, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)N(R^4)_2$, $C_{0-6}alkylSR^4$, $C_{0-6}alkyl(SO_2)N(R^4)_2$, $OC_{2-6}alkylN-R^4(SO_2)R^4$, $C_{0-6}alkyl(SO)N(R^4)_2$, OSO_2R^4, SO_3R^4, $C_{0-6}alkylNR^4(SO_2)N(R^4)_2$, $C_{0-6}alkylN-R^4(SO)R^4$, $C_{0-6}alkylSO_2R^4$, $C_{0-6}alkylSOR^4$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkyl-C_{3-6}cycloalkyl$, $C_{0-6}alkylC_{3-6}cycloalkenyl$, $C_{0-6}alkylC_6cycloalkynyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, and $C_{0-6}alkylheterocyclyl$, wherein said $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, or $C_{0-6}alkyl-heterocyclyl$ is optionally substituted with one or more R^6;

R^4 is selected from hydrogen, $C_{1-6}alkyl$, $C_{1-3}haloalkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylC_{3-6}cycloalkenyl$, $C_{0-6}alkylC_6cycloalkynyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, $C_{0-6}alkylheterocyclyl$, $C_{1-6}alkylOR^5$, and $C_{1-6}alkylN(R^5)_2$, wherein

said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkyl-heteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^4 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S; said heterocyclic ring optionally being substituted with one or more R^6;

R^5 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheterocyclyl and C_{0-6}alkylheteroaryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^5 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^6 is selected from oxo, halogen, nitro, CN, OR^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylheterocyclyl, C_{1-6}halo-alkyl, OC_{2-6}alkyl$N(R^7)_2$, $N(R^7)_2$, $CON(R^7)_2$, $NR^7(CO)R^7$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^7, $SON(R^7)_2$, $(SO_2)N(R^7)_2$, $NR^7SO_2R^7$, NR^7SOR^7, SO_2R^7, SOR^7, $(CO)C_{1-6}$alkyl-$N(R^7)_2$, $(SO_2)C_{1-6}$alkyl$N(R^7)_2$, OSO_2R^7 and SO_3R^7, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, or C_{0-6}alkylC_{3-6}cyclo-alkyl is optionally substituted with one or more substituents selected from halo, nitro, cyano, OR^7, C_{1-6}alkyl, or C_{1-6}haloalkyl;

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cyclo-alkyl, C_{3-6}cycloalkenyl, C_6cycloalkynyl, aryl, heteroaryl and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one to three substituents selected from hydroxy, cyano, halogen and OC_{1-3}alkyl; or two R^7 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring being optionally substituted with one or more substituents selected from hydroxy, OC_{1-3}alkyl, cyano and halogen.

3. A compound according to claim 1, wherein

A is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{0-6}alkylC_{3-8}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl or C_{0-6}alkylC_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;

B is aryl or heteroaryl; wherein said aryl or heteroaryl is optionally substituted with one or more R^2;

C is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkyl-CN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, C_{0-6}alkyl$(SO)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO_2)N(R^4)_2$, C_{0-6}alkyl$NR^4(SO)R^4$, SF_5, and OSF_5, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkyl-C_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkyl-heterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, C_{0-6}alkylOR^4, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, CHO, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)OR^4$, $O(CO)R^4$, $O(CO)N(R^4)_2$, $NR^4(CO)OR^4$, C_{0-6}alkyl$NR^4(CO)R^4$, $NR^4(CO)N(R^4)_2$, $NR^4(CO)(CO)R^4$, $NR^4(CO)(CO)$-$N(R^4)_2$, C_{0-6}alkylSR^4, C_{0-6}alkylOSO_2R^4, C_{0-6}alkylSO_3R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, SF_5, and OSF_5, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl or is optionally substituted with one or more R^3;

R^2 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkyl-C_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkyl-heterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4,

CHO, NO_2, C_{0-6}alkylCON(R^4)$_2$, O(CO)OR^4, O(CO)R^4, O(CO)N(R^4)$_2$, NR^4(CO)OR^4, C_{0-6}alkylNR^4(CO)R^4, NR^4(CO)N(R^4)$_2$, NR^4(CO)(CO)R^4, NR^4(CO)(CO)N(R^4)$_2$, C_{0-6}alkyl-(SO)N(R^4)$_2$, C_{0-6}alkylNR^4(SO_2)N(R^4)$_2$, C_{0-6}alkylNR^4(SO)R^4 and C_{0-6}alkylOR^4, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkyl-heteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3;

R^3 is selected from halogen, NO_2, CHO, C_{0-6}alkylCN, C_{0-6}alkylOR^4, C_{1-6}haloalkyl, C_{0-6}alkylN(R^4)$_2$, NR^4C(O)R^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkylCON(R^4)$_2$, C_{0-6}alkylNR^4(CO)R^4, O(CO)N(R^4)$_2$, NR^4(CO)OR^4, NR^4(CO)N(R^4)$_2$, O(CO)OR^4, O(CO)R^4, C_{0-6}alkylCOR^4, NR^4(CO)(CO)R^4, NR^4(CO)(CO)N(R^4)$_2$, C_{0-6}alkylSR^4, C_{0-6}alkyl(SO_2)N(R^4)$_2$, OC_{2-6}alkyl-NR^4(SO_2)R^4, C_{0-6}alkyl(SO)N(R^4)$_2$, OSO_2R^4, SO_3R^4, C_{0-6}alkylNR^4(SO_2)N(R^4)$_2$, C_{0-6}alkylN-R^4(SO)R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkyl-C_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, and C_{0-6}alkylheterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkyl-heterocyclyl is optionally substituted with one or more R^6;

R^4 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{1-6}alkylOR^5, and C_{1-6}alkylN(R^5)$_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkyl-heteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^4 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S; said heterocyclic ring optionally being substituted with one or more R^6;

R^5 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylC_6cycloalkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheterocyclyl and C_{0-6}alkylheteroaryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkyl-C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;

R^6 is selected from oxo, halogen, nitro, CN, OR^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylheterocyclyl, C_{1-6}haloalkyl, OC_{2-6}alkyl$N(R^7)_2$, $N(R^7)_2$, $CON(R^7)_2$, $NR^7(CO)R^7$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^7, $SON(R^7)_2$, $(SO_2)N(R^7)_2$, $NR^7SO_2R^7$, NR^7SOR^7, SO_2R^7, SOR^7, $(CO)C_{1-6}$alkyl$N(R^7)_2$, $(SO_2)C_{1-6}$alkyl$N(R^7)_2$, OSO_2R^7 and SO_3R^7, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, or C_{0-6}alkylC_{3-6}cycloalkyl is optionally substituted with one or more substituents selected from halo, nitro, cyano, OR^7, C_{1-6}alkyl, or C_{1-6}haloalkyl;

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_6cycloalkynyl, aryl, heteroaryl and heterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one to three substituents selected from hydroxy, cyano, halogen and OC_{1-3}alkyl; or two R^7 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring being optionally substituted with one or more substituents independently selected from hydroxy, OC_{1-3}alkyl, cyano and halogen.

4. A compound according to claim 1, wherein

A is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{0-6}alkylC_{3-8}cycloalkyl, C_{0-6}alkylC_{5-6}cycloalkenyl, or C_{0-6}alkyl-C_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;

B is aryl or heteroaryl; wherein said aryl or heteroaryl is optionally substituted with one or more R^2;

C is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{3-6}cycloalkenyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)R^4$, C_{0-6}alkyl$NR^4(CO)R^4$, C_{0-6}alkylSR^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl,

C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylC_{5-6}cycloalkenyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, C_{0-6}alkylOR^4, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)R^4$, C_{0-6}alkyl$NR^4(CO)R^4$, C_{0-6}alkylSR^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl or is optionally substituted with one or more R^3; or two R^1 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^2 is selected from C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkylCOR^4, NO_2, C_{0-6}alkyl$CON(R^4)_2$, $O(CO)R^4$, C_{0-6}alkylSR^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, and C_{0-6}alkylOR^4, wherein said C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^3,
or two R^2 may together with the atoms to which they are attached form a cyclic or heterocyclic ring optionally substituted with one or more R^6;

R^3 is selected from halogen, NO_2, C_{0-6}alkylCN, C_{0-6}alkylOR^4, C_{1-6}haloalkyl, C_{0-6}alkyl$N(R^4)_2$, $NR^4C(O)R^4$, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$CON(R^4)_2$, C_{0-6}alkyl$NR^4(CO)R^4$, $O(CO)R^4$, C_{0-6}alkylCOR^4, C_{0-6}alkylSR^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, and C_{0-6}alkylheterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;

R^4 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{1-6}alkylOR^5, and C_{1-6}alkyl$N(R^5)_2$,

wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6; or two R^4 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S; said heterocyclic ring optionally being substituted with one or more R^6;

R^5 is selected from hydrogen, C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheterocyclyl and C_{0-6}alkylheteroaryl, wherein said C_{1-6}alkyl, C_{0-6}alkyl-C_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more R^6;
or two R^5 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring optionally being substituted with one or more R^6;

R^6 is selected from oxo, halogen, nitro, CN, OR^7, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylheterocyclyl, C_{1-6}haloalkyl, OC_{2-6}alkyl$N(R^7)_2$, $N(R^7)_2$, $CON(R^7)_2$, $NR^7(CO)R^7$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^7, SO_2R^7, SOR^7, wherein said C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl or C_{0-6}alkylC_{3-6}cycloalkyl is optionally substituted with one or more substituents independently selected from halo, nitro, cyano, OR^7, C_{1-6}alkyl, C_{1-3}haloalkyl, or OC_{1-3}haloalkyl;

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{3-6}cycloalkyl, aryl, heteroaryl and heterocyclyl, wherein said C_{1-6}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one to three substituents independently selected from hydroxy, cyano, halogen and OC_{1-3}alkyl; or two R^7 may together form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, said heterocyclic ring being optionally substituted with one or more substituents independently selected from hydroxy, OC_{1-3}alkyl, cyano and halogen;

as a free base or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4, wherein said B is phenyl or heteroaryl.

6. A compound according to any one of claims 1 to 5, wherein B is not substituted.

7. A compound according to any one of claims 1 to 5, wherein B is substituted.

8. A compound according to claim 7, wherein R^2 is C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, halogen, C_{0-6}alkylCN or C_{0-6}alkylOR^4.

9. A compound according to claim 8, wherein R^2 is fluoro, OR^4 or C_{1-6}alkyl.

10. A compound according to any one of claims 1 to 9, wherein R^4 is hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{0-6}alkylC_{3-6}cycloalkyl or C_{0-6}alkylheteroaryl.

11. A compound according to claim 11, wherein R^4 is hydrogen, C_{1-6}alkyl or C_{1-3}haloalkyl.

12. A compound according to any one of claims 1 to 11, wherein A is C_{1-6}alkyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{0-6}alkylC_{3-8}cycloalkyl, or C_{0-6}alkylC_{3-8}heterocyclyl.

13. A compound according to claim 12, wherein A is C_{0-6}alkylC_{3-8}cycloalkyl or C_{0-6}alkyl-C_{3-8}heterocyclyl.

14. A compound according to any one of claims 1 to 13, wherein A is not substituted.

15. A compound according to any one of claims 1 to 13, wherein A is substituted.

16. A compound according to claim 15, wherein R^1 is C_{1-6}alkyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylOR^4, halogen, C_{0-6}alkylCN or C_{0-6}alkylCOR^4.

17. A compound according to claim 16, wherein R^1 is C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylOR^4, halogen or C_{0-6}alkylCOR^4.

18. A compound according to any one of claims 14 to 17, wherein said C_{1-6}alkyl is methyl or ethyl.

19. A compound according to any one of claims 1 to 18, wherein C is hydrogen, C_{1-6}alkyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN or C_{0-6}alkyl$NR^4(CO)R^4$.

20. A compound according to any one of claims 1 to 19, wherein R^3 is halogen, NO_2, C_{0-6}alkylCN, C_{0-6}alkylOR^4, C_{1-6}haloalkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkyl-C_{3-6}cycloalkyl or C_{0-6}alkylheterocyclyl.

21. A compound according to claim 20, wherein R^3 is halogen, C_{2-6}alkynyl, CN or OR^4.

22. A compound according to claim 20, wherein R^3 is halogen or C_{2-4}alkynyl.

23. A compound according to any one of claims 1-22, wherein R^6 is oxo, halogen, CN, OR^7, C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl or C_{1-6}haloalkyl.

24. A compound according to claim 23, wherein R^6 is chloro.

25. A compound according to claim 1, wherein
A is selected from C_{1-6}alkyl, C_{1-6}alkylaryl, C_{0-6}alkylC_{3-8}cycloalkyl and C_{0-6}alkylC_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;
B is aryl;
C is C_{0-6}alkylaryl or C_{0-6}alkylheteroaryl, wherein said C_{0-6}alkylaryl or C_{0-6}alkylheteroaryl is optionally substituted with one or more R^1;
R^1 C_{0-6}alkylCOR^4;
R^3 is C_{0-6}alkylOR^4; and
R^4 is C_{1-6}alkyl.

26. A compound according to claim 1, wherein

A is C_{0-6}alkylC_{3-8}cycloalkyl or C_{0-6}alkyl-C_{3-8}heterocyclyl, wherein said A is optionally substituted with one or more R^1;

B is aryl or heteroaryl; wherein said aryl or heteroaryl is optionally substituted with one or more R^2;

C is hydrogen, C_{1-6}alkyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{0-6}alkylheterocyclyl, C_{0-6}alkylOR^4, C_{0-6}alkylCO_2R^4, C_{0-6}alkyl$N(R^4)_2$, halogen, C_{0-6}alkylCN, C_{0-6}alkyl$NR^4(CO)R^4$;

R^1 is C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylOR^4, halogen or C_{0-6}alkylCOR^4;

R^2 is C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, halogen, C_{0-6}alkylCN or C_{0-6}alkylOR^4;

R^3 is halogen, C_{2-6}alkynyl, CN or OR^4;

R^4 is hydrogen, C_{1-6}alkyl, C_{1-3}haloalkyl, C_{0-6}alkylC_{3-6}cycloalkyl or C_{0-6}alkylheteroaryl;

R^6 is oxo, halogen, CN, OR^7, C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl or C_{1-6}haloalkyl.

27. A compound selected from

2-(3'-Methoxybiphenyl-3-yl)-2,5-dimethyl-2H-imidazol-4-amine;

(R)-2-(3'-Methoxybiphenyl-3-yl)-2,5-dimethyl-2H-imidazol-4-amine;

2,5-Dimethyl-2-(3-(pyridin-3-yl)phenyl)-2H-imidazol-4-amine;

2-Ethyl-5-methyl-2-(3-(pyridin-3-yl)phenyl)-2H-imidazol-4-amine;

2-Cyclohexyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine;

2-Cyclohexyl-5-methyl-2-(3-(pyridin-3-yl)phenyl)-2H-imidazol-4-amine;

2-(3'-Methoxybiphenyl-3-yl)-5-methyl-2-(tetrahydro-2H-pyran-4-yl)-2H-imidazol-4-amine;

1-(4-(4-Amino-2-(3'-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)piperidin-1-yl)ethanone;

2-Benzyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine; and

(R)-2-Benzyl-5-methyl-2-(3-(pyrimidin-5-yl)phenyl)-2H-imidazol-4-amine;

(R)- and (S)- 2-(2'-fluoro-3'-methoxybiphenyl-3-yl)-5-methyl-2-(pyridin-3-ylmethyl)-2H-imidazol-4-amine;

(R)- and (S)- 2-(3-(5-Chloropyridin-3-yl)phenyl)-5-methyl-2-(pyridin-3-ylmethyl)-2H-imidazol-4-amine;

2-(3-Bromophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine;

2-(3-(5-Chloropyridin-3-yl)phenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine;
2-Cyclopropyl-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-4-amine;
5-(4-Amino-2-(3-bromophenyl)-5-methyl-2H-imidazol-2-yl)-3-methylpyridin-2(1H)-one;
5-(4-Amino-2-(3-(5-chloropyridin-3-yl)phenyl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;
5-(4-Amino-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;
5-(4-Amino-2-(3'-methoxybiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;
5-(4-Amino-2-(3',5'-difluorobiphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;
2-(3-(5-Chloropyridin-3-yl)-4-fluorophenyl)-2-cyclopropyl-5-methyl-2H-imidazol-4-amine;
2-Cyclopropyl-2-(4-fluoro-3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-5-methyl-2H-imidazol-4-amine;
2-(3-(5-Chloropyridin-3-yl)phenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine;
2-(3-(5-Fluoropyridin-3-yl)phenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine;
2-(3-(5-Methoxypyridin-3-yl)phenyl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine;
2-(3'-Methoxybiphenyl-3-yl)-5-methyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-2H-imidazol-4-amine;
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)phenyl)pyrazine-2-carboxamide;
2-(3-(5-Chloropyridin-3-yl)phenyl)-2-cyclobutyl-5-methyl-2H-imidazol-4-amine;
2-Cyclobutyl-2-(3-(5-fluoropyridin-3-yl)phenyl)-5-methyl-2H-imidazol-4-amine;
2-Cyclobutyl-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-4-amine;
2-(3-(5-Chloropyridin-3-yl)phenyl)-2-isopropyl-5-methyl-2H-imidazol-4-amine;
2-(3-(5-Fluoropyridin-3-yl)phenyl)-2-isopropyl-5-methyl-2H-imidazol-4-amine;
2-Isopropyl-5-methyl-2-(3-(5-(prop-1-ynyl)pyridin-3-yl)phenyl)-2H-imidazol-4-amine;
2-Cyclohexyl-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine;

2-Cycloheptyl-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine;
2-(Bicyclo[2.2.1]heptan-2-yl)-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine;
2-Cyclooctyl-2-(4-methoxyphenyl)-5-methyl-2H-imidazol-4-amine;
2-(4-Methoxyphenyl)-5-methyl-2-(3-phenylpropyl)-2H-imidazol-4-amine;
2-(4-Methoxyphenyl)-2-(3-(3-methoxyphenyl)propyl)-5-methyl-2H-imidazol-4-amine;
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2'-fluoro-5'-methoxybiphenyl-2-ol;
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-5'-chloro-2'-fluorobiphenyl-2-ol;
5'-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-6-fluoro-2'-hydroxybiphenyl-3-carbonitrile;
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2'-fluoro-3'-methoxybiphenyl-2-ol;
4-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(5-(prop-1-ynyl)pyridin-3-yl)phenol;
4-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(pyrazin-2-yl)phenol;
4-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2-(4-(prop-1-ynyl)pyridin-2-yl)phenol;
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2',5'-dichlorobiphenyl-2-ol;
5-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-2'-chloro-5'-methoxybiphenyl-2-ol;
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-4-fluorophenyl)-5-chloropicolinamide;
3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-N-(3-chlorophenyl)benzamide;
3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)-N-(4-chlorophenyl)benzamide;
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)phenyl)-4-chloropicolinamide;
N-(3-(4-Amino-2-cyclopropyl-5-methyl-2H-imidazol-2-yl)phenyl)-5-chloropicolinamide;
5-(4-Amino-5-methyl-2-(3'-(prop-1-ynyl)biphenyl-3-yl)-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;
5-(4-Amino-2-(2'-fluoro-5'-(prop-1-ynyl)biphenyl-3-yl)-5-methyl-2H-imidazol-2-yl)-1-ethyl-3-methylpyridin-2(1H)-one;
as a free base or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising as active ingredient a therapeutically effective amount of a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, in association with pharmaceutically acceptable excipients, carriers or diluents.

29. A compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, for use as a medicament.

30. A compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, for treating or preventing an Aβ-related pathology.

31. A compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, for treating or preventing an Aβ-related pathology, wherein said Aβ-related pathology is Downs syndrome, a β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, a disorder associated with cognitive impairment, MCI ("mild cognitive impairment"), Alzheimer Disease, memory loss, attention deficit symptoms associated with Alzheimer disease, neurodegeneration associated with Alzheimer Disease, dementia of mixed vascular origin, dementia of degenerative origin, pre-senile dementia, senile dementia, dementia associated with Parkinson's disease, progressive supranuclear palsy or cortical basal degeneration.

32. A compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, for treating or preventing Alzheimer Disease.

33. A compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing an Aβ-related pathology.

34. Use of a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing an Aβ-related pathology, wherein said Aβ-related pathology is Downs syndrome, a β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, a disorder

associated with cognitive impairment, MCI ("mild cognitive impairment"), Alzheimer Disease, memory loss, attention deficit symptoms associated with Alzheimer disease, neurodegeneration associated with Alzheimer disease, dementia of mixed vascular origin, dementia of degenerative origin, pre-senile dementia, senile dementia, dementia associated with Parkinson's disease, progressive supranuclear palsy or cortical basal degeneration.

35. Use of a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing Alzheimer's Disease.

36. A method of inhibiting activity of BACE comprising contacting said BACE with a compound of any one of claims 1 to 27.

37. A method of treating or preventing an Aβ-related pathology in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof.

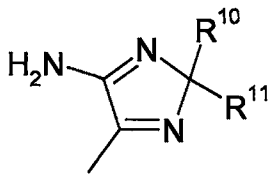
38. The method of claim 37, wherein said Aβ-related pathology is Downs syndrome, a β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, a disorder associated with cognitive impairment, MCI ("mild cognitive impairment"), Alzheimer Disease, memory loss, attention deficit symptoms associated with Alzheimer disease, neurodegeneration associated with Alzheimer disease, dementia of mixed vascular origin, dementia of degenerative origin, pre-senile dementia, senile dementia, dementia associated with Parkinson's disease, progressive supranuclear palsy or cortical basal degeneration.

39. A method of treating or preventing Alzheimer's Disease in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof.

40. A method of treating or preventing an Aβ-related pathology in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a

compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, and at least one cognitive enhancing agent, memory enhancing agent, or choline esterase inhibitor.

41. A process for preparing a compound of formula (VI)

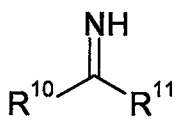


(VI)

wherein R^{10} and R^{11} are defined as A and B in claim 1, or wherein R^{10} and R^{11} are defined as groups that can be converted to A and B in subsequent transformations;

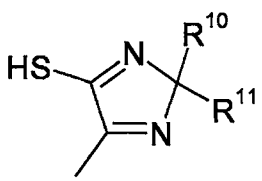
comprising the steps of

a) reacting a compound of formula (III)



(III)

with 2-oxopropane thioamide to yield a compound of formula (V)



(V)

and

b) treating a compound of formula (V) with ammonia, optionally in the presence of an oxidation agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050760

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:A61K, A61P, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007058601 A1 (ASTRAZENECA AB ET AL), 24 May 2007 (2007-05-24); claims 48-59; ex 16	1-41
A	WO 2008076045 A1 (ASTRAZENECA AB ET AL), 26 June 2008 (2008-06-26); claims 1, 27-43; ex 10	1-41
A	US 20080287460 A1 (BURROWS JEREMY NICHOLAS ET AL), 20 November 2008 (2008-11-20); claims 1, 32-38	1-41
A	WO 2008076043 A1 (ASTRAZENECA AB ET AL), 26 June 2008 (2008-06-26); claims 23-37; ex 22,23	1-41
A	WO 2007058602 A2 (ASTRAZENECA AB ET AL), 24 May 2007 (2007-05-24); claims 31-41; 4,54	1-41

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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05-10-2010	05-10-2010

Name and mailing address of the ISA/SE	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050760

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☒ Claims Nos.: 36-40
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 36-40 relate to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/SE2010/050760

Continuation of: second sheet

International Patent Classification (IPC)

C07D 401/10 (2006.01)
A61K 31/4178 (2006.01)
A61P 25/00 (2006.01)
C07D 233/88 (2006.01)
C07D 403/10 (2006.01)

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Cited literature, if any, will be enclosed in paper form.

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