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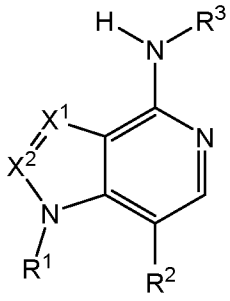
(54) Title: OGA INHIBITOR COMPOUNDS

(57) Abstract: The present invention relates to O-GlcNAc hydrolase (OGA) inhibitors. The invention is also directed to pharmaceutical compositions comprising such compounds, to processes for preparing such compounds and compositions, and to the use of such compounds and compositions for the prevention and treatment of disorders in which inhibition of OGA is beneficial, such as tauopathies, in particular Alzheimer's disease or progressive supranuclear palsy; and neurodegenerative diseases accompanied by a tau pathology, in particular amyotrophic lateral sclerosis or frontotemporal lobe dementia caused by C9ORF72 mutations.

OGA INHIBITOR COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to O-GlcNAc hydrolase (OGA) inhibitors, having the structure shown in Formula (I)



(I)

wherein the radicals are as defined in the specification. The invention is also directed to pharmaceutical compositions comprising such compounds, to processes for preparing such compounds and compositions, and to the use of such compounds and compositions for the prevention and treatment of disorders in which inhibition of OGA is beneficial, such as tauopathies, in particular Alzheimer's disease or progressive supranuclear palsy; and neurodegenerative diseases accompanied by a tau pathology, in particular amyotrophic lateral sclerosis or frontotemporal lobe dementia caused by C9ORF72 mutations; or alpha synucleinopathies, in particular Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, or alpha synucleinopathy caused by Gaucher's disease.

BACKGROUND OF THE INVENTION

O-GlcNAcylation is a reversible modification of proteins where N-acetyl-D-glucosamine residues are transferred to the hydroxyl groups of serine- and threonine residues yield O-GlcNAcylated proteins. More than 1000 of such target proteins have been identified both in the cytosol and nucleus of eukaryotes. The modification is thought to regulate a huge spectrum of cellular processes including transcription, cytoskeletal processes, cell cycle, proteasomal degradation, and receptor signalling.

O-GlcNAc transferase (OGT) and O-GlcNAc hydrolase (OGA) are the only two proteins described that add (OGT) or remove (OGA) O-GlcNAc from target proteins.

OGA was initially purified in 1994 from spleen preparation and 1998 identified as antigen expressed by meningiomas and termed MGEA5, consists of 916 amino (102915 Dalton) as a monomer in the cytosolic compartment of cells. It is to be distinguished from ER- and Golgi-related glycosylation processes that are important for trafficking and secretion of proteins and different to OGA have an acidic pH optimum, whereas OGA display highest activity at neutral pH.

The OGA catalytic domain with its double aspartate catalytic center resides in the N-terminal part of the enzyme which is flanked by two flexible domains. The C-terminal part consists of a putative HAT (histone acetyl transferase domain) preceded by a stalk domain. It has yet still to be proven that the HAT-domain is catalytically active.

O-GlcNAcylated proteins as well as OGT and OGA themselves are particularly abundant in the brain and neurons suggesting this modification plays an important role in the central nervous system. Indeed, studies confirmed that *O*-GlcNAcylation represents a key regulatory mechanism contributing to neuronal communication, memory formation and neurodegenerative disease. Moreover, it has been shown that OGT is essential for embryogenesis in several animal models and *ogt* null mice are embryonic lethal. OGA is also indispensible for mammalian development. Two independent studies have shown that OGA homozygous null mice do not survive beyond 24-48 hours after birth. *Oga* deletion has led to defects in glycogen mobilization in pups and it caused genomic instability linked cell cycle arrest in MEFs derived from homozygous knockout embryos. The heterozygous animals survived to adulthood however they exhibited alterations in both transcription and metabolism.

It is known that perturbations in *O*-GlcNAc cycling impact chronic metabolic diseases such as diabetes, as well as cancer. *Oga* heterozygosity suppressed intestinal tumorigenesis in an *Apc-/+* mouse cancer model and the *Oga* gene (*MGEA5*) is a documented human diabetes susceptibility locus.

In addition, O-GlcNAc-modifications have been identified on several proteins that are involved in the development and progression of neurodegenerative diseases and a correlation between variations of O-GlcNAc levels on the formation of neurofibrillary tangle (NFT) protein by Tau in Alzheimer's disease has been suggested. In addition, O-GlcNAcylation of alpha-synuclein in Parkinson's disease has been described (Levine, PM, et al. PNAS January 29, 2019, Vol. 116, No. 5, pp 1511-1519; Lewis, YE et al. ACS Chem Biol. 2017 Apr 21, Vol. 2, No. 4, pp 1020-1027; Marotta, NP et al. Nat Chem. 2015 Nov, Vol. No. 11, pp. 913-20).

In the central nervous system six splice variants of tau have been described. Tau is

encoded on chromosome 17 and consists in its longest splice variant expressed in the central nervous system of 441 amino acids. These isoforms differ by two N-terminal inserts (exon 2 and 3) and exon 10 which lie within the microtubule binding domain. Exon 10 is of considerable interest in tauopathies as it harbours multiple mutations that render tau prone to aggregation as described below. Tau protein binds to and stabilizes the neuronal microtubule cytoskeleton which is important for regulation of the intracellular transport of organelles along the axonal compartments. Thus, tau plays an important role in the formation of axons and maintenance of their integrity. In addition, a role in the physiology of dendritic spines has been suggested as well.

Tau aggregation is either one of the underlying causes for a variety of so called tauopathies like PSP (progressive supranuclear palsy), Down's syndrome (DS), FTLD (frontotemporal lobe dementia), FTDP-17 (frontotemporal dementia with Parkinsonism-17), Pick's disease (PD), CBD (corticobasal degeneration), agryophilic grain disease (AGD), and AD (Alzheimer's disease). In addition, tau pathology accompanies additional neurodegenerative diseases like amyotrophic lateral sclerosis (ALS) or FTLD cause by C9ORF72 mutations. In these diseases, tau is post-translationally modified by excessive phosphorylation which is thought to detach tau from microtubules and makes it prone to aggregation. O-GlcNAcylation of tau regulates the extent of phosphorylation as serine or threonine residues carrying O-GlcNAc-residues are not amenable to phosphorylation. This effectively renders tau less prone to detaching from microtubules and reduces aggregation into neurotoxic tangles which ultimately lead to neurotoxicity and neuronal cell death. This mechanism may also reduce the cell-to-cell spreading of tau-aggregates released by neurons via along interconnected circuits in the brain which has recently been discussed to accelerate pathology in tau-related dementias. Indeed, hyperphosphorylated tau isolated from brains of AD-patients showed significantly reduced O-GlcNAcylation levels.

An OGA inhibitor administered to JNPL3 tau transgenic mice successfully reduced NFT formation and neuronal loss without apparent adverse effects. This observation has been confirmed in another rodent model of tauopathy where the expression of mutant tau found in FTD can be induced (tg4510). Dosing of a small molecule inhibitor of OGA was efficacious in reducing the formation of tau-aggregation and attenuated the cortical atrophy and ventricle enlargement.

Moreover, the O-GlcNAcylation of the amyloid precursor protein (APP) favours processing via the non-amyloidogenic route to produce soluble APP fragment and avoid cleavage that results in the AD associated amyloid-beta (Aβ) formation.

Maintaining O-GlcNAcylation of tau by inhibition of OGA represents a potential approach to decrease tau-phosphorylation and tau-aggregation in neurodegenerative diseases mentioned above thereby attenuating or stopping the progression of neurodegenerative tauopathy-diseases.

WO2012/117219 (Summit Corp. plc., published 7 September 2012) describes N-[[5-(hydroxymethyl)pyrrolidin-2-yl]methyl]alkylamide and N-alkyl-2-[5-(hydroxymethyl)pyrrolidin-2-yl]acetamide derivatives as OGA inhibitors.

WO2014/159234 (Merck Patent GMBH, published 2 October 2014) discloses mainly 4-phenyl or benzyl-piperidine and piperazine compounds substituted at the 1-position with an acetamido-thiazolylmethyl or acetamidoxazolylmethyl substituent and the compound N-[5-[(3-phenyl-1-piperidyl)methyl]thiazol-2-yl]acetamide;

WO2016/0300443 (Asceneuron S.A., published 3 March 2016), WO2017/144633 and WO2017/0114639 (Asceneuron S.A., published 31 August 2017) disclose 1,4-disubstituted piperidines or piperazines as OGA inhibitors;

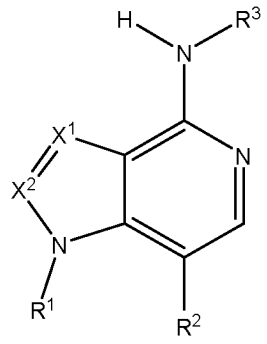
WO2017/144637 (Asceneuron S.A, published 31 August 2017) discloses more particular 4-substituted 1-[1-(1,3-benzodioxol-5-yl)ethyl]-piperazine; 1-[1-(2,3-dihydrobenzofuran-5-yl)ethyl]-; 1-[1-(2,3-dihydrobenzofuran-6-yl)ethyl]-; and 1-[1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]-piperazine derivatives as OGA inhibitors;

WO2017/106254 (Merck Sharp & Dohme Corp.) describes substituted N-[5-[(4-methylene-1-piperidyl)methyl]thiazol-2-yl]acetamide; WO2018/217558 (Eli Lilly and Company) describes 5-methyl-1,3,4-oxadiazol-2-yl and WO2019/178191 (Biogen Ma Inc) discloses [(hetero)aryl-3-ylmethyl]pyrrolidin-1-ylmethyl- and [(hetero)aryl-3-ylmethyl]piperidin-1-ylmethyl- derivative compounds as OGA inhibitors; and WO2018/140299 (Eli Lilly and Company) discloses N-[fluoro-5-[[(2S,4S)-2-methyl-4-[(5-methyl-1,2,4-oxadiazol-3-yl)methoxy[-1-piperidyl]methyl]thiazol-2-yl]acetamide as OGA inhibitor.

There is still a need for OGA inhibitor compounds with an advantageous balance of properties, for example with improved potency, good bioavailability, pharmacokinetics, and brain penetration, and/or better toxicity profile. It is accordingly an object of the present invention to provide compounds that overcome at least some of these problems.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula (I)



(I),

and the tautomers and the stereoisomeric forms thereof, and the deuterated forms thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of C_{1-6}alkyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, $-C(=O)NR^xR^y$, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents, wherein the 5-or 6-membered heteroaryl is optionally substituted with one or two independently selected C_{1-4}alkyl substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

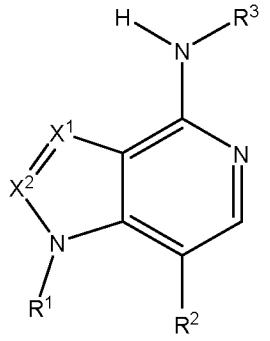
(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy;

and the pharmaceutically acceptable salts and the solvates thereof,

for use as a medicament; in particular for use as a medicament for the prevention or treatment of a tauopathy, in particular a tauopathy selected from the group consisting of Alzheimer's disease, progressive supranuclear palsy, Down's syndrome, frontotemporal lobe dementia, frontotemporal dementia with Parkinsonism-17, Pick's disease, corticobasal degeneration, and agryophilic grain disease; or a neurodegenerative disease accompanied by a tau pathology, in particular a neurodegenerative disease selected from amyotrophic lateral sclerosis or frontotemporal lobe dementia caused by C9ORF72 mutations or for use in preventing or treating a disorder selected from an alpha synucleinopathy, in particular Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, or alpha synucleinopathy caused by Gaucher's disease, in a subject in need thereof.

The present invention also relates to compounds of Formula (I)



(I),

and the tautomers and the stereoisomeric forms thereof, and the deuterated forms thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, -C(=O)NR^xR^y, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents, wherein the 5-or 6-membered heteroaryl is optionally substituted with one or two independently selected C_{1-4}alkyl substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy;

and the pharmaceutically acceptable salts and the solvates thereof,

Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. An illustration of the invention is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. Illustrating the invention is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier.

Exemplifying the invention are methods of preventing or treating a disorder mediated by the inhibition of O-GlcNAc hydrolase (OGA), comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Further exemplifying the invention are methods of inhibiting OGA, comprising administering to a subject in need thereof a prophylactically or a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

An example of the invention is a method of preventing or treating a disorder selected from a tauopathy, in particular a tauopathy selected from the group consisting of Alzheimer's disease, progressive supranuclear palsy, Down's syndrome, frontotemporal lobe dementia, frontotemporal dementia with Parkinsonism-17, Pick's disease, corticobasal degeneration, and agryophilic grain disease; or a neurodegenerative disease accompanied by a tau pathology, in particular a neurodegenerative disease selected from amyotrophic lateral sclerosis or frontotemporal lobe dementia caused by C9ORF72 mutations, or preventing or treating a disorder selected from an alpha synucleinopathy, in particular Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, or alpha synucleinopathy caused by Gaucher's disease, comprising administering to a subject in need thereof, a prophylactically or a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Another example of the invention is any of the compounds described above for use in preventing or treating a tauopathy, in particular a tauopathy selected from the group consisting of Alzheimer's disease, progressive supranuclear palsy, Down's syndrome, frontotemporal lobe dementia, frontotemporal dementia with Parkinsonism-17, Pick's disease, corticobasal degeneration, and agryophilic grain disease; or a neurodegenerative disease accompanied by a tau pathology, in particular a neurodegenerative disease selected from amyotrophic lateral sclerosis or frontotemporal lobe dementia caused by C9ORF72 mutations or for use in preventing or treating a disorder selected from an alpha synucleinopathy, in particular Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, or alpha synucleinopathy caused by Gaucher's disease,, in a subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of Formula (I), as defined herein before, and pharmaceutically acceptable addition salts and solvates thereof. The compounds of Formula (I) are inhibitors of O-GlcNAc hydrolase (OGA) and may be useful in the prevention or treatment of tauopathies, in particular a tauopathy selected from the group consisting of Alzheimer's disease, progressive supranuclear palsy, Down's syndrome, frontotemporal lobe dementia, frontotemporal dementia with Parkinsonism-17, Pick's disease, corticobasal degeneration, and agryophilic grain

disease; or maybe useful in the prevention or treatment of neurodegenerative diseases accompanied by a tau pathology, in particular a neurodegenerative disease selected from amyotrophic lateral sclerosis or frontotemporal lobe dementia caused by C9ORF72 mutations; or may be useful in the prevention or treatment of alpha synucleinopathies, in particular Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, or alpha synucleinopathy caused by Gaucher's disease.

In a particular embodiment, the invention is directed to compounds of Formula (I) as referred to herein, and the tautomers and the stereoisomeric forms thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, $-C(=O)NR^xR^y$, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy.

In a further particular embodiment, the invention is directed to compounds of Formula (I) as referred to herein, and the tautomers and the stereoisomeric forms thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, -C(=O)NR^xR^y, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) a 1H-indazolyl radical, optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy.

In a further embodiment, the invention is directed to compounds of Formula (I) as referred to herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^1 is selected from the group consisting of -C_{1-4}alkyl-C(=O)NR^xR^y optionally substituted with one or more halo substituents; unsubstituted C_{2-6}alkyl; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl,

triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl.

In a further embodiment, the invention is directed to compounds of Formula (I) as referred to herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^1 is -C_{1-4}alkyl-C(=O)NR^xR^y optionally substituted with one or more halo substituents; wherein R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl.

In a further embodiment, the invention is directed to compounds of Formula (I) as referred to herein, and the tautomers and the stereoisomeric forms thereof, wherein

R^1 is -C_{1-4}alkyl-C(=O)NR^xR^y , in particular -CH_2-C(=O)NR^xR^y, optionally substituted with one or more halo substituents; wherein R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl and C_{3-6}cycloalkyl.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^1 is -C_{1-4}alkyl-C(=O)NR^xR^y, in particular -CH_2-C(=O)NR^xR^y, optionally substituted with one or more halo substituents; wherein R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and polyhaloC_{1-4}alkyl, in particular hydrogen and C_{1-4}alkyl.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, oxazolyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, oxazolyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents; and pyridinyl optionally substituted with halo or C_{1-4}alkyl; with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl; and C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents; with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl, in particular C_{4-6}alkyl; and C_{1-6}alkyl substituted with one or more substituents, each independently selected from halo.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^1 is selected from the group consisting of C_{1-6}alkyl

substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, -$C(=O)NR^xR^y$, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^1 is selected from the group consisting of -C_{1-4}alkyl-$C(=O)NR^xR^y$ optionally substituted with one or more halo substituents; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl.

In yet a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^1 is selected from a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl,

pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl.

In yet a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^1 is selected from a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl and imidazolyl, each of which may be optionally substituted with or two substituents each independently selected from C_{1-4}alkyl.

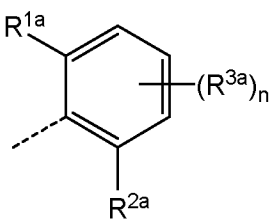
In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^3 is selected from the group consisting of

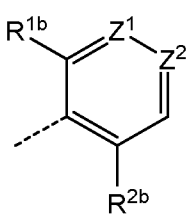
(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

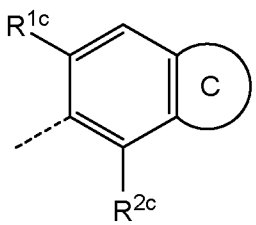
(b) 1H-indazolyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, and C_{1-4}alkyloxy.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^3 is selected from the group consisting of (a), (b), and (c):







(a) (b) (c)

wherein R^{1a}, R^{2a}, R^{1b} and R^{2b} are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; with the proviso that at least one of R^{1a} or R^{2a}, and at least one of R^{1b} or R^{2b} is not hydrogen;

Z^1 and Z^2 are each independently selected from N, CH or CR^{3b}, with the proviso that at least one of Z^1 or Z^2 is N;

R^{3a} and R^{3b} when present, are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; wherein

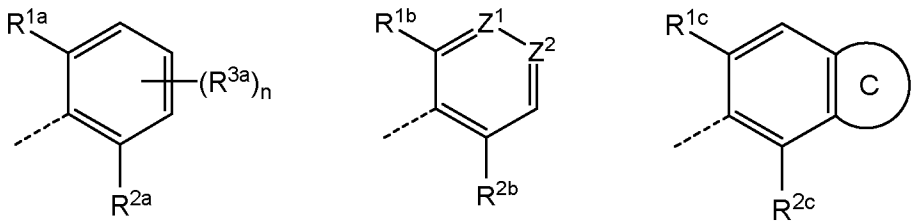
n represents 0, 1 or 2;

Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, and C_{1-4}alkyloxy;

R^{1c} and R^{2c} are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, and -(C=O)C_{1-4}alkyl; and

C forms a fused 5-membered heteroaromatic ring selected from the group consisting of pyrazolyl, and imidazolyl, each being optionally substituted with one or more independently selected C_{1-4}alkyl substituents.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^3 is selected from the group consisting of (a), (b), and (c):



(a) (b) (c)

wherein R^{1a}, R^{2a}, R^{1b} and R^{2b} are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -CN, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; with the proviso that at least one of R^{1a} or R^{2a}, and at least one of R^{1b} or R^{2b} is not hydrogen;

Z^1 and Z^2 are each independently selected from N, CH or CR^{3b}, with the proviso that at least one of Z^1 or Z^2 is N;

R^{3a} and R^{3b} when present, are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; wherein

n represents 0 or 1;

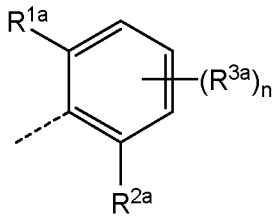
Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, and C_{1-4}alkyloxy;

R^{1c} and R^{2c} are each hydrogen; and

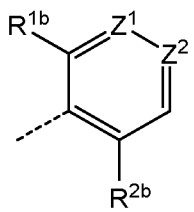
C forms a fused 5-membered heteroaromatic ring selected from pyrazolyl optionally substituted with one C_{1-4}alkyl.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein

R^3 is selected from the group consisting of (a) and (b):



(a)



(b)

wherein R^{1a}, R^{2a}, R^{1b} and R^{2b} are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; with the proviso that at least one of R^{1a} or R^{2a}, and at least one of R^{1b} or R^{2b} is not hydrogen;

Z^1 and Z^2 are each independently selected from N, CH or CR^{3b}, with the proviso that at least one of Z^1 or Z^2 is N;

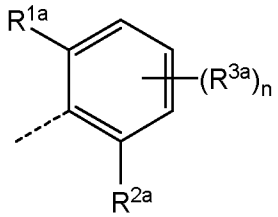
R^{3a} and R^{3b} when present, are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; wherein

n represents 0, 1 or 2; and

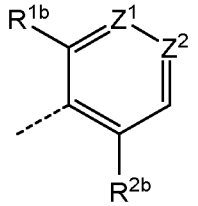
Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, and C_{1-4}alkyloxy.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein

R^3 is selected from the group consisting of (a) and (b):



(a)



(b)

wherein R^{1a}, R^{2a}, R^{1b} and R^{2b} are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

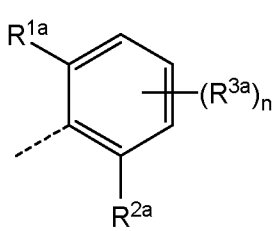
Z^1 and Z^2 are each independently selected from N, CH or CR^{3b}, with the proviso that at least one of Z^1 or Z^2 is N;

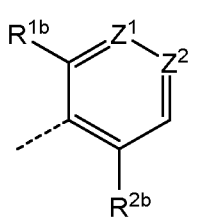
R^{3a} and R^{3b} when present, are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; wherein

n represents 0, 1 or 2; and

Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, and C_{1-4}alkyloxy.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^3 is group (a) or (b):





(a) (b)

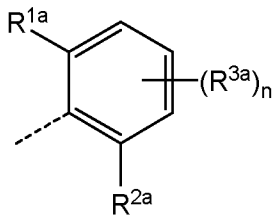
wherein R^{1a}, R^{2a}, R^{1b} and R^{2b} are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, and polyhaloC_{1-4}alkyloxy;

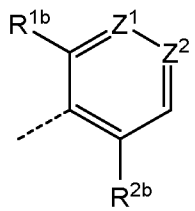
Z^1 and Z^2 are each independently selected from N, CH or CR^{3b}, with the proviso that at least one of Z^1 or Z^2 is N; and

R^{3a} and R^{3b} when present, are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, and polyhaloC_{1-4}alkyloxy; wherein

n represents 0, 1 or 2.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^3 is group (a) or (b):





(a) (b)

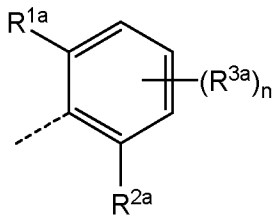
wherein R^{1a}, R^{2a}, R^{1b} and R^{2b} are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, and polyhaloC_{1-4}alkyloxy;

Z^1 and Z^2 are each independently selected from N, CH or CR^{3b}, with the proviso that at least one of Z^1 or Z^2 is N; and

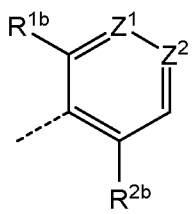
R^{3a} and R^{3b} when present, are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, and polyhaloC_{1-4}alkyloxy; wherein

n represents 0, 1 or 2.

In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, wherein R^3 is group (a) or (b):



(a)



(b)

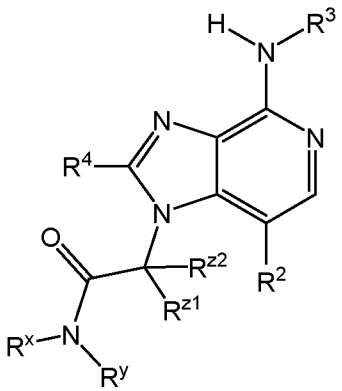
wherein R^{1a}, R^{2a}, R^{1b} and R^{2b} are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, and polyhaloC_{1-4}alkyloxy;

Z^1 and Z^2 are each independently selected from N, CH or CR^{3b}, with the proviso that at least one of Z^1 or Z^2 is N; and

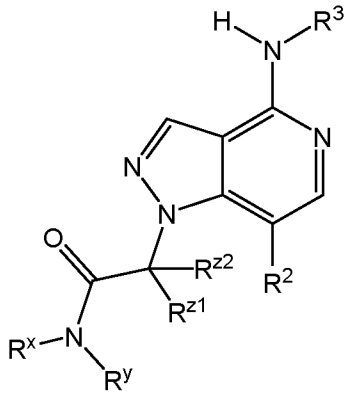
R^{3a} and R^{3b} when present, are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, and polyhaloC_{1-4}alkyloxy; wherein

n represents 0 or 1.

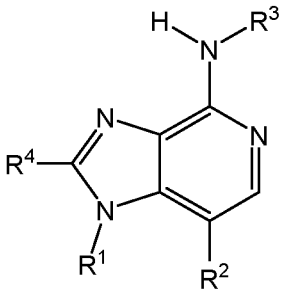
In a further embodiment, the invention is directed to compounds of Formula (I) as described herein, having the Formulae (I-A), (I-B), (I-C) or (I-D)



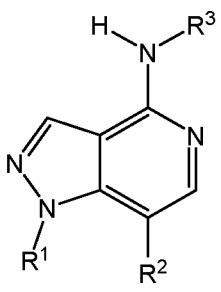
(I-A)



(I-B)



(I-C)



(I-D)

wherein each of the variables are as defined herein, and z1 and z2 are each independently selected from hydrogen, deuterium and halogen, in particular hydrogen.

DEFINITIONS

"Halo" shall denote fluoro, chloro and bromo; "C_{1-4}alkyl" and "C_{1-6}alkyl" shall denote a straight or branched saturated alkyl group having 1, 2, 3 or 4 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, respectively e.g. methyl, ethyl, 1-propyl, 2-propyl, butyl, 1-methyl-propyl, 2-methyl-1-propyl, 1,1-dimethylethyl, and the like; "C_{1-4}alkyloxy" shall denote an ether radical wherein C_{1-4}alkyl is as defined before; "mono- and polyhaloC_{1-4}alkyl" as used herein alone or as part of another group, refers to C_{1-4}alkyl as defined before, substituted with 1, 2, 3 or where possible with more halo atoms as defined before; "mono- or polyhaloC_{1-4}alkyloxy" shall denote an ether radical wherein mono or polyhaloC_{1-4}alkyl is as defined before.

In general, whenever the term "substituted" is used in the present invention, it is meant, unless otherwise indicated or is clear from the context, to indicate that one or more hydrogens, in particular 1 to 3 hydrogens, preferably 1 or 2 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using "substituted" are replaced with a selection of substituents from the indicated group, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who is or has been the object of treatment, observation or experiment. As used herein, the term "subject" therefore encompasses patients, as well as asymptomatic or presymptomatic individuals at risk of developing a disease or condition as defined herein.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. The term "prophylactically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that substantially reduces the potential for onset of the disease or disorder being prevented.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

Hereinbefore and hereinafter, the term “compound of Formula (I)” is meant to include the addition salts, the solvates and the stereoisomers thereof.

The terms “stereoisomers” or “stereochemically isomeric forms” hereinbefore or hereinafter are used interchangeably.

The invention includes all stereoisomers of the compound of Formula (I) either as a pure stereoisomer or as a mixture of two or more stereoisomers.

Enantiomers are stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture. Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, i.e. they are not related as mirror images. If a compound contains a double bond, the substituents may be in the E or the Z configuration. If a compound contains a disubstituted cycloalkyl group, the substituents may be in the cis or trans configuration. Therefore, the invention includes enantiomers, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers and mixtures thereof.

The absolute configuration is specified according to the Cahn-Ingold-Prelog system. The configuration at an asymmetric atom is specified by either R or S. Resolved compounds whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light.

When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, i.e. associated with less than 50%, preferably less than 20%, more preferably less than 10%, even more preferably less than 5%, in particular less than 2% and most preferably less than 1%, of the other isomers. Thus, when a compound of formula (I) is for instance specified as (R), this means that the compound is substantially free of the (S) isomer; when a compound of formula (I) is for instance specified as E, this means that the compound is substantially free of the Z isomer; when a compound of formula (I) is for instance specified as cis, this means that the compound is substantially free of the trans isomer.

For use in medicine, the addition salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable addition salts". Other salts may, however, be useful in the preparation of compounds according to this invention or of their

pharmaceutically acceptable addition salts. Suitable pharmaceutically acceptable addition salts of the compounds include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable addition salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts.

Representative acids which may be used in the preparation of pharmaceutically acceptable addition salts include, but are not limited to, the following: acetic acid, 2,2-dichloroactic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4- acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucoronic acid, L-glutamic acid, beta-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5- disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, L- pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoromethylsulfonic acid, and undecylenic acid.
Representative bases which may be used in the preparation of pharmaceutically acceptable addition salts include, but are not limited to, the following: ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, dimethylethanol-amine, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylene-diamine, *N*-methyl-glucamine, hydrabamine, 1*H*-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, secondary amine, sodium hydroxide, triethanolamine, tromethamine and zinc hydroxide.

The names of compounds were generated according to the nomenclature rules agreed upon by the Chemical Abstracts Service (CAS) or according to the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC).

PHARMACOLOGY

The compounds of the present invention and the pharmaceutically acceptable compositions thereof inhibit O-GlcNAc hydrolase (OGA) and therefore may be useful in the treatment or prevention of diseases involving tau pathology, also known as tauopathies, and diseases with tau inclusions. Such diseases include, but are not limited to Alzheimer's disease, amyotrophic lateral sclerosis and parkinsonism-dementia complex, argyrophilic grain disease, chronic traumatic encephalopathy, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by MAPT mutations), Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations), Gerstmann-Sträussler-Scheinker disease, Parkinson's disease, Guadeloupean parkinsonism, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, and white matter tauopathy with globular glial inclusions.

The compounds of the present invention and the pharmaceutically acceptable compositions thereof inhibit O-GlcNAc hydrolase (OGA) and therefore may be also useful in the treatment or prevention of diseases involving an alpha synucleinopathy, in particular Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, or alpha synucleinopathy caused by Gaucher's disease.

As used herein, the term "treatment" is intended to refer to all processes, wherein there may be a slowing, interrupting, arresting or stopping of the progression of a disease or an alleviation of symptoms, but does not necessarily indicate a total elimination of all symptoms. As used herein, the term "prevention" is intended to refer to all processes, wherein there may be a slowing, interrupting, arresting or stopping of the onset of a disease.

The invention also relates to a compound according to the general Formula (I), a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt thereof, for use in the treatment or prevention of diseases or conditions selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis and parkinsonism-dementia complex, argyrophilic grain disease, chronic traumatic encephalopathy, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by MAPT mutations), Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations), Gerstmann-Sträussler-Scheinker disease, Guadeloupean parkinsonism, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, white matter tauopathy with globular glial inclusions, Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, and alpha synucleinopathy caused by Gaucher's disease.

The invention also relates to a compound according to the general Formula (I), a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt thereof, for use in the treatment, prevention, amelioration, control or reduction of the risk of diseases or conditions selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis and parkinsonism-dementia complex, argyrophilic grain disease, chronic traumatic encephalopathy, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by MAPT mutations), Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations), Gerstmann-Sträussler-Scheinker disease, Guadeloupean parkinsonism, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, white matter tauopathy with globular glial inclusions, Parkinson's disease, dementia due to Parkinson's (or

neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, and alpha synucleinopathy caused by Gaucher's disease.In particular, the diseases or conditions may in particular be selected from a tauopathy, more in particular a tauopathy selected from the group consisting of Alzheimer's disease, progressive supranuclear palsy, Down's syndrome, frontotemporal lobe dementia, frontotemporal dementia with Parkinsonism-17, Pick's disease, corticobasal degeneration, and agryophilic grain disease; or the diseases or conditions may in particular be neurodegenerative diseases accompanied by a tau pathology, more in particular a neurodegenerative disease selected from amyotrophic lateral sclerosis or frontotemporal lobe dementia caused by C9ORF72 mutations.

In particular, the diseases or conditions may in particular be selected from an alpha synuclinopathy, more in particular a tauopathy selected from the group consisting of Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, and alpha synucleinopathy caused by Gaucher's disease.

Preclinical states in Alzheimer's and tauopathy diseases:

In recent years the United States (US) National Institute for Aging and the International Working Group have proposed guidelines to better define the preclinical (asymptomatic) stages of AD (Dubois B, et al. Lancet Neurol. 2014;13:614-629; Sperling, RA, et al. Alzheimers Dement. 2011;7:280-292). Hypothetical models postulate that Aβ accumulation and tau-aggregation begins many years before the onset of overt clinical impairment. The key risk factors for elevated amyloid accumulation, tau-aggregation and development of AD are age (i.e, 65 years or older), *APOE* genotype, and family history. Approximately one third of clinically normal older individuals over 75 years of age demonstrate evidence of Aβ or tau accumulation on PET amyloid and tau imaging studies, the latter being less advanced currently. In addition, reduced Abeta-levels in CSF measurements are observed, whereas levels of non-modified as well as phosphorylated tau are elevated in CSF. Similar findings are seen in large autopsy studies and it has been shown that tau aggregates are detected in the brain as early as 20 years of age and younger. Amyloid-positive (Aβ+) clinically normal individuals consistently demonstrate evidence of an "AD-like endophenotype" on other biomarkers, including disrupted functional network activity in both functional magnetic resonance imaging (MRI) and resting state connectivity, fluorodeoxyglucose ^{18}F (FDG) hypometabolism, cortical thinning, and accelerated rates of atrophy. Accumulating longitudinal data also strongly suggests that Aβ+ clinically normal individuals are at increased risk for cognitive decline and progression to mild

cognitive impairment (MCI) and AD dementia. The Alzheimer's scientific community is of the consensus that these Aβ+ clinically normal individuals represent an early stage in the continuum of AD pathology. Thus, it has been argued that intervention with a therapeutic agent that decreases Aβ production or the aggregation of tau is likely to be more effective if started at a disease stage *before* widespread neurodegeneration has occurred. A number of pharmaceutical companies are currently testing BACE inhibition in prodromal AD.

Thanks to evolving biomarker research, it is now possible to identify Alzheimer's disease at a preclinical stage before the occurrence of the first symptoms. All the different issues relating to preclinical Alzheimer's disease such as, definitions and lexicon, the limits, the natural history, the markers of progression and the ethical consequences of detecting the disease at the asymptomatic stage, are reviewed in Alzheimer's & Dementia 12 (2016) 292-323.

Two categories of individuals may be recognized in preclinical Alzheimer's disease or tauopathies. Cognitively normal individuals with amyloid beta or tau aggregation evident on PET scans, or changes in CSF Abeta, tau and phospho-tau are defined as being in an "asymptomatic at-risk state for Alzheimer's disease (AR-AD)" or in a "asymptomatic state of tauopathy". Individuals with a fully penetrant dominant autosomal mutation for familial Alzheimer's disease are said to have "presymptomatic Alzheimer's disease". Dominant autosomal mutations within the tau-protein have been described for multiple forms of tauopathies as well.

Thus, in an embodiment, the invention also relates to a compound according to the general Formula (I), a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt thereof, for use in control or reduction of the risk of preclinical Alzheimer's disease, prodromal Alzheimer's disease, or tau-related neurodegeneration as observed in different forms of tauopathies.

Prodromal states of Parkinson's disease have also been studied. Thus, in an embodiment, the invention also relates to a compound according to the general Formula (I), a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt thereof, for use in control or reduction of the risk of prodromal Parkinson's disease.

As already mentioned hereinabove, the term "treatment" does not necessarily indicate a total elimination of all symptoms, but may also refer to symptomatic treatment in any of the disorders mentioned above. In view of the utility of the compound of Formula (I), there is provided a method of treating subjects such as warm-blooded animals,

including humans, suffering from or a method of preventing subjects such as warm-blooded animals, including humans, suffering from any one of the diseases mentioned hereinbefore.

Said methods comprise the administration, i.e. the systemic or topical administration, preferably oral administration, of a prophylactically or a therapeutically effective amount of a compound of Formula (I), a stereoisomeric form thereof, a pharmaceutically acceptable addition salt or solvate thereof, to a subject such as a warm-blooded animal, including a human.

Therefore, the invention also relates to a method for the prevention and/or treatment of any of the diseases mentioned hereinbefore comprising administering a prophylactically or a therapeutically effective amount of a compound according to the invention to a subject in need thereof.

The invention also relates to a method for modulating O-GlcNAc hydrolase (OGA) activity, comprising administering to a subject in need thereof, a prophylactically or a therapeutically effective amount of a compound according to the invention and as defined in the claims or a pharmaceutical composition according to the invention and as defined in the claims.

A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day. In these methods of treatment the compounds according to the invention are preferably formulated prior to administration. As described herein below, suitable pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

The compounds of the present invention, that can be suitable to treat or prevent any of the disorders mentioned above or the symptoms thereof, may be administered alone or in combination with one or more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of Formula (I) and one or more additional therapeutic agents, as well as administration of the compound of Formula (I) and each additional therapeutic agent in its own separate pharmaceutical dosage formulation. For example, a compound of Formula (I) and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate oral dosage formulations.

A skilled person will be familiar with alternative nomenclatures, nosologies, and classification systems for the diseases or conditions referred to herein. For example, the fifth edition of the Diagnostic & Statistical Manual of Mental Disorders (DSM-5^{TM}) of

the American Psychiatric Association utilizes terms such as neurocognitive disorders (NCDs) (both major and mild), in particular, neurocognitive disorders due to Alzheimer's disease. Such terms may be used as an alternative nomenclature for some of the diseases or conditions referred to herein by the skilled person.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides compositions for preventing or treating diseases in which inhibition of O-GlcNAc hydrolase (OGA) is beneficial, such as Alzheimer's disease, progressive supranuclear palsy, Down's syndrome, frontotemporal lobe dementia, frontotemporal dementia with Parkinsonism-17, Pick's disease, corticobasal degeneration, agryophilic grain disease, amyotrophic lateral sclerosis, frontotemporal lobe dementia caused by C9ORF72 mutations, Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, or alpha synucleinopathy caused by Gaucher's disease, said compositions comprising a therapeutically effective amount of a compound according to formula (I) and a pharmaceutically acceptable carrier or diluent.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. Accordingly, the present invention further provides a pharmaceutical composition comprising a compound according to the present invention, together with a pharmaceutically acceptable carrier or diluent. The carrier or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The pharmaceutical compositions of this invention may be prepared by any methods well known in the art of pharmacy. A therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as oral, percutaneous or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars,

kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The exact dosage and frequency of administration depends on the particular compound of Formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

Depending on the mode of administration, the pharmaceutical composition will comprise from 0.05 to 99% by weight, preferably from 0.1 to 70% by weight, more preferably from 0.1 to 50% by weight of the active ingredient, and, from 1 to 99.95%

by weight, preferably from 30 to 99.9% by weight, more preferably from 50 to 99.9% by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

The present compounds can be used for systemic administration such as oral, percutaneous or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. The compounds are preferably orally administered. The exact dosage and frequency of administration depends on the particular compound according to Formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

The amount of a compound of Formula (I) that can be combined with a carrier material to produce a single dosage form will vary depending upon the disease treated, the mammalian species, and the particular mode of administration. However, as a general guide, suitable unit doses for the compounds of the present invention can, for example, preferably contain between 0.1 mg to about 1000 mg of the active compound. A preferred unit dose is between 1 mg to about 500 mg. A more preferred unit dose is between 1 mg to about 300 mg. Even more preferred unit dose is between 1 mg to about 100 mg. Such unit doses can be administered more than once a day, for example, 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total dosage for a 70 kg adult is in the range of 0.001 to about 15 mg per kg weight of subject per administration. A preferred dosage is 0.01 to about 1.5 mg per kg weight of subject per administration, and such therapy can extend for a number of weeks or months, and in some cases, years. It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs that have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those of skill in the area.

A typical dosage can be one 1 mg to about 100 mg tablet or 1 mg to about 300 mg taken once a day, or, multiple times per day, or one time-release capsule or tablet taken once a day and containing a proportionally higher content of active ingredient. The time-release effect can be obtained by capsule materials that dissolve at different pH

values, by capsules that release slowly by osmotic pressure, or by any other known means of controlled release.

It can be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to start, interrupt, adjust, or terminate therapy in conjunction with individual patient response.

The invention also provides a kit comprising a compound according to the invention, prescribing information also known as "leaflet", a blister package or bottle, and a container. Furthermore, the invention provides a kit comprising a pharmaceutical composition according to the invention, prescribing information also known as "leaflet", a blister package or bottle, and a container. The prescribing information preferably includes advice or instructions to a patient regarding the administration of the compound or the pharmaceutical composition according to the invention. In particular, the prescribing information includes advice or instruction to a patient regarding the administration of said compound or pharmaceutical composition according to the invention, on how the compound or the pharmaceutical composition according to the invention is to be used, for the prevention and/or treatment of a tauopathy in a subject in need thereof. Thus, in an embodiment, the invention provides a kit of parts comprising a compound of Formula (I) or a stereoisomeric for thereof, or a pharmaceutically acceptable salt or a solvate thereof, or a pharmaceutical composition comprising said compound, and instructions for preventing or treating a tauopathy. The kit referred to herein can be, in particular, a pharmaceutical package suitable for commercial sale.

For the compositions, methods and kits provided above, one of skill in the art will understand that preferred compounds for use in each are those compounds that are noted as preferred above. Still further preferred compounds for the compositions, methods and kits are those compounds provided in the non-limiting Examples below.

EXPERIMENTAL PART

Hereinafter, the term "m.p." means melting point, "min" means minutes, "ACN" means acetonitrile, "aq." means aqueous, "BrettPhos" means [(2-Di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′- triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′ -biphenyl)]palladium(II) methanesulfonate methanesulfonate, "DAST" means (diethylamino)sulfur trifluoride, "DCM" means dichloromethane, "DIAD" means diisopropylazodicarboxylate, "DIPE" means diisopropyl ether, "DMF" means

dimethylformamide, "DMA" means N,N-dimethylacetamide, "DMSO" means dimethylsulfoxide, "EDC-HCl" means N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride, "FCC" means flash column chromatography, "HOBt" means 1-hydroxybenzotriazole, "OL" means organic layer, "$PdCl_2(dppf)_2$" means [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane, "$Pd(PPh_3)_4$" means tetrakis(triphenylphosphine)palladium(0), "$Pd_2(dba)_3$" means tris(dibenzylideneacetone)dipalladium(0), "X-Phos" means 2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl, "Xant-Phos" means 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, "r.t." or "RT" means room temperature, "rac" or "RS" means racemic, "LC-MS" means liquid chromatography/mass spectrometry, "HPLC" means high-performance liquid chromatography, "r.m." means reaction mixture, "RP" means reversed phase, "R_t" means retention time (in minutes), "MIK" means methyl isobutyl ketone, "$[M+H]^+$" means the protonated mass of the free base of the compound, "wt" means weight, "EtOAc" means ethyl acetate, "MeOH" means methanol, "NCS" means N-chlorosuccinimide, "RBF" means round bottom flask, "sat" means saturated, "soltn" or "sol." means solution, "THF" means tetrahydrofuran, "TPP" means triphenylphosphine.

Whenever the notation "RS" is indicated herein, it denotes that the compound is a racemic mixture at the indicated centre, unless otherwise indicated. The stereochemical configuration for centres in some compounds has been designated "*R*" or "*S*" when the mixture(s) was separated; for some compounds, the stereochemical configuration at indicated centres has been designated as "*R**" or "*S**" when the absolute stereochemistry is undetermined although the compound itself has been isolated as a single stereoisomer and is enantiomerically/diastereomerically pure. The enantiomeric excess of compounds reported herein was determined by analysis of the racemic mixture by supercritical fluid chromatography (SFC) followed by SFC comparison of the separated enantiomer(s).

Microwave assisted reactions were performed in a single-mode reactor: InitiatorTM Sixty EXP microwave reactor (Biotage AB).

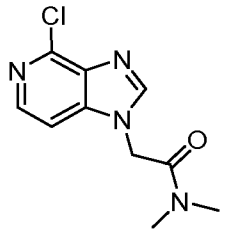
Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck) using reagent grade solvents. Open column chromatography was performed on silica gel, particle size 60 Å, mesh = 230-400 (Merck) using standard techniques.

Automated flash column chromatography was performed using ready-to-connect cartridges, on irregular silica gel, particle size 15-40 μm (normal phase disposable flash columns) on different flash systems: either a SPOT or LAFLASH systems from Armen

Instrument, or PuriFlash® 430evo systems from Interchim, or 971-FP systems from Agilent, or Isolera 1SV systems from Biotage.

INTERMEDIATE 1

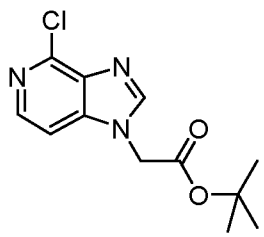
2-(4-Chloro-1H-imidazo[4,5-c]pyridin-1-yl)-N,N-dimethylacetamide



K_2CO_3 (22.73 g, 164 mmol) was added to a stirred suspension of 4-chloro-1H-imidazo[4,5-c]pyridine (21.05 g, 0.14 mol) in DMF (426 ml) at RT under a nitrogen atmosphere. Then, 2-chloro-N,N-dimethylacetamide (14.83 mL, 0.14 mol) in DMF (100 ml) was added dropwise and the mixture was stirred at 70° C for 16h. Then, the mixture was filtered and washed with CH_3CN. The filtered cake was discarded, and the filtrate was evaporated in vacuo. To the residue was added DCM and the solid was filtered off and washed with DCM to yield a light-yellow solid. The filtrate was evaporated and to the residue was added again DCM. The solid was filtered off and washed with DMC to yield as a greenish solid. Both solids were purified by flash column chromatography separately (silica; 7M solution of ammonia in MeOH in DCM 0/100 to 7/93). The desired fractions were collected and evaporated in vacuo to yield I-1 as a solid (14.94 g, 46 %).

INTERMEDIATE 2

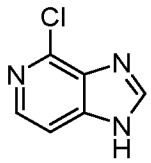
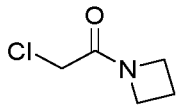
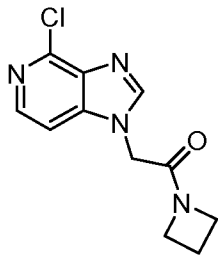
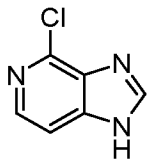
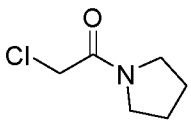
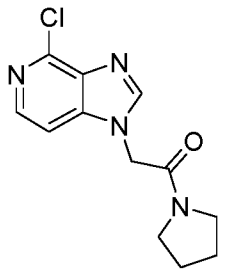
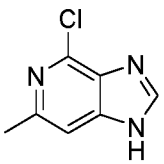
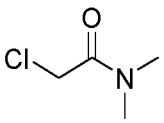
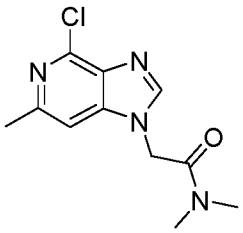
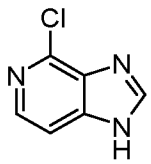
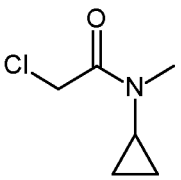
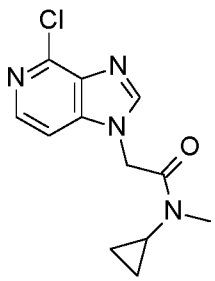
tert-Butyl 2-(4-chloro-1H-imidazo[4,5-c] pyridin-1-yl)acetate

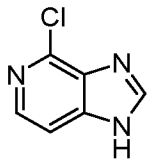
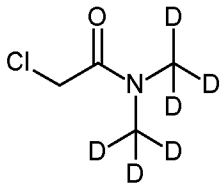
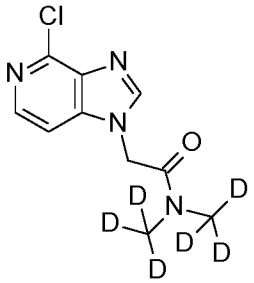
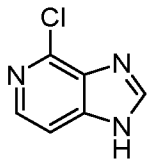
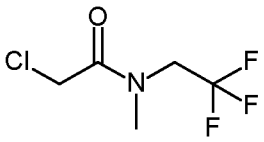
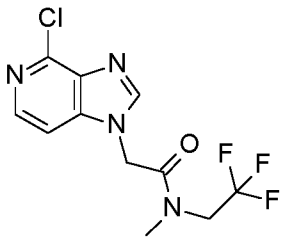
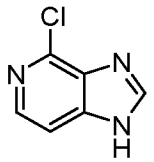
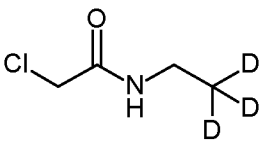
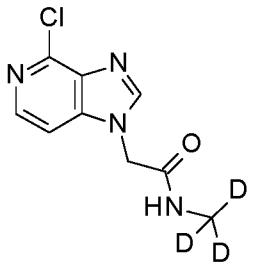


To a mixture of DMF (40 mL), 4-cloro-1H-imidazo(4,5-c) pyridine (1.0 g, 6.5 mmol) and K_2CO_3 (1.5 g, 6.51 mmol) was added tert-butyl bromoacetate (1.18 mL, 7.81 mmol) and this was stirred for 16 h at RT The solvent was evaporated in vacuo and the residue was dissolved in EtOAc and water. The organic layer was washed with water (x2) and brine, then separated, dried (MgSO4), filtered and the solvents evaporated in vacuo. The

crude was purified by flash column chromatography (silica, EtOAc in heptane 0/100 to 80/20) to yield I-2 (1.25 g, 66%) as a solid, after trituration from DIPE .

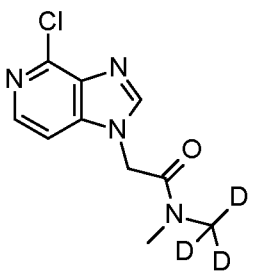
The following Intermediates were synthesized in an analogous manner from the indicated Intermediates and reagents:

Starting material	Reagent	Intermediate
 [2770-01-6]	 [63177-41-3]	 I-3
 [2770-01-6]	 [20266-00-6]	 I-4
 [860258-50-0]	 [2675-89-0]	 I-5 (alternative synthesis)
 [2770-01-6]	 [722538-31-0]	 I-6

Starting material	Reagent	Intermediate
 [2770-01-6]	 I-7	 I-8
 [2770-01-6]	 [1179829-40-3]	 I-9
 [2770-01-6]	 I-10	 I-11

INTERMEDIATE 12

2-(4-Chloroimidazo[4,5-c]pyridin-1-yl)-N-methyl-N-(trideuteriomethyl)acetamide

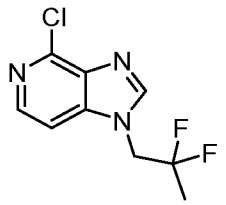


Sodium hydride [7646-69-7] (60% dispersion in mineral oil, 39 mg, 0.97 mmol) was added to a stirred solution of I-11 (200 mg, 0.89 mmol) in dry N,N-dimethylformamide [68-12-2] (3 mL) at 0 °C under nitrogen. The mixture was stirred

for 5 min, iodomethane [74-884] (60 µL, 2.28 g/mL, 0.97 mmol) was added and the RM was stirred at RT for 20 h. After this time, the mixture was quenched with sat aq NH4Cl soln and the AQ phase was extracted with EtOAc. The organic layer was separated, dried over MgSO4, filtered and the solvents evaporated in vacuo. The resulting residue was purified by flash column chromatography on silica gel, using as eluent a gradient MeOH in DCM 0/100 to 7/95 to yield I-12 (91% purity, 64%) as a white solid.

INTERMEDIATE 13

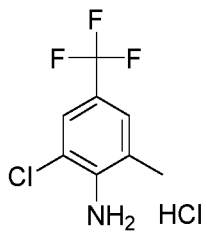
4-Chloro-1-(2,2-difluoropropyl)-1H-imidazo[4,5-c] pyridine



DIAD (0.96 mL, 4.9 mmol) was added to a stirred and cooled (0 ° C) solution of 4-chloro-1H-imidazo[4,5-c] pyridine (0.50 g, 3.26 mmol), 2,2-difluoropropanol (0.47 g, 4.88 mmol) and TPP (1.28 g, 4.88 mmol) in THF (80 mL) at 0 °C. The mixture was stirred at 0°C for 30 min and then at RT. No product was formed. The mixture was heated to 60 °C overnight. 2 isomers were observed. The product was purified on silica gel, eluent: 0-2% MeOH in DCM. With this eluent system, the more polar isomer was the desired isomer. The other isomer was eluted from the column first and co-eluted with triphenylphosphine-oxide and was not purified. The more polar, desired isomer was re-purified on RP: Stationary phase: RP XBridge Prep C18 OBD-10µm, 30x150mm, Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN. The pure fractions were evaporated to give I-13 (130 mg, 17%)

INTERMEDIATE 14

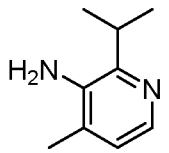
2-Chloro-6-methyl-4-(trifluoromethyl)aniline hydrochloride



To a stirred solution (20 °C) of 2-methyl-4-(trifluoromethyl) aniline (5 g, 0.029 mol) in DMF (50 mL) was added in small portions NCS (4.28 g, 0.031 mol). The ensuing solution was heated to 50 °C for 2 h then cooled and concentrated in vacuo. The residue was diluted with DCM and treated with saturated K_2CO_3 solution (2x) and the OL was dried over $MgSO_4$, filtered and concentrated in vacuo to afford a tan oil which still contained DMF. This was purified by silica gel chromatography using an 80 g redisep flash column eluting with 0-40% EtOAc in heptane to afford a tan oil (5.6 g, yield 93.6%). This was dissolved in DIPE and treated with 6M HCl in i-PrOH and stirred overnight. The bright white solid was collected by filtration and dried to afford I-14 (5.6 g, yield 80%).

INTERMEDIATE 15

2-Isopropyl-4-methylpyridin-3-amine



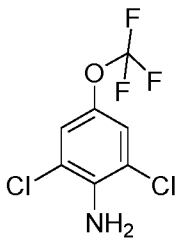
$Pd(PPh_3)_4$ (45.1 g, 39.0 mmol) was added to a mixture of 2-bromo-4-methylpyridin-3-amine (73.0 g, 390 mmol) and isopropenylboronic acid pinacol ester (78.7 g, 468 mmol) in dioxane (741 mL) and aq $NaHCO_3$ solution (742 mL, 1 M, 742 mmol) in a 3-necked RBF under a flow of N_2. The RM was stirred at 100 °C overnight, then it was cooled to RT, filtered through Celite®, washed with EtOAc and the layers separated. The aqueous layer was extracted again with EtOAc (2x) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product as dark yellow oil. The crude product was dissolved in DCM, then cooled to 0 °C and then HCl (400 mL, 2 M, 800 mmol) was added and the resulting mixture stirred at 0 °C for 20 min. The aqueous layer was extracted again with EtOAc (2x) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum to provide the crude product as dark yellow oil. The crude product was dissolved in DCM, then cooled to 0 °C and then HCl (400 mL, 2 M, 800 mmol) was added and the resulting mixture stirred at 0 °C for 20 min. The aqueous layer was separated, then extracted with DCM (3x). The combined aqueous layers were placed in a round bottom flask, mixed with DCM (200 mL) then cooled to 0 °C. Na_2CO_3 (87 g, 82 mmol) was added portion wise, stirred 5 min, then 100 mL water added. The resulting mixture was stirred for 20 min, then the organic layer was separated. The aqueous layer was extracted with DCM (2x). The combined organic layers were dried ($MgSO_4$), filtered and

evaporated, to yield 4-methyl-2-(prop-1-en-2-yl)pyridin-3-amine (55.7 g, 96%), which was used as such in the next step.

To a solution of 4-methyl-2-(prop-1-en-2-yl)pyridin-3-amine (24.0 g, 0.162 mol) in EtOH, 687 mL) was added Pd/C (10%, 2.1 g, 1.9 mmol), this was then stirred under an H_2 atmosphere for 8 hours. The suspension was filtered through Celite®, and concentrated in vacuo to yield a yellow oil (24 g). This was purified on silica gel, using as eluent a gradient of 0-2% MeOH in DCM. The desired fractions were collected, and the solvent evaporated, to give I-15 as an oil (18.8 g, 77%).

INTERMEDIATE 16

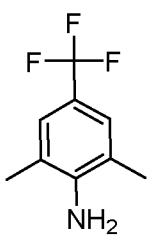
2,6-Dichloro-4-(trifluoromethoxy)aniline



4-(Trifluoromethoxy) aniline (1.15 mL, 1.31 g/mL, 8.47 mmol) was dissolved in DMF (27 mL). NCS (1.24 g, 9.32 mmol) was added and then the reaction was stirred at 60°C for 4 hr. Additional NCS (0.1 eq.) was added, and the mixture was stirred another 2 h at 60°C. The mixture was diluted with sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 20/80). The desired fractions were collected and concentrated in vacuo to yield I-16 as an orange viscous solid (1.97 g, yield 93%).

INTERMEDIATE 17

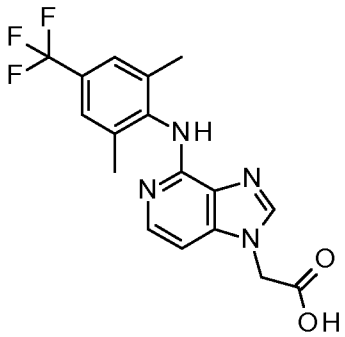
2,6-Dimethyl-4-(trifluoromethyl)aniline



A mixture of 2,6-dibromo-4-(trifluoromethyl)aniline [72678-19-4] (63.8 g, 200 mmol) in dry THF (1000 mL) in a 3 L 4-necked flask was degassed for 10 min with nitrogen. Bis(tri-tert-butylphosphine)palladium(0) [53199-31-8] (3.0 g, 5.87 mmol) was added and then methylzinc chloride [5158-46-3] (300 mL, 2 M, 600 mmol) was added with a syringe (exothermic reaction, temp. 50°C) and the mixture was stirred while cooling to room temp for 1h. The r.m. was carefully decomposed with 100 ml of water. The solution was filtered through Dicalite® and the organics were evaporated (30°C, 100 mm Hg). To this aqueous residue more water (200 mL) was added, and the residue was extracted with DCM, and then the organic layer was dried on $MgSO_4$, filtered and evaporated. The residue was distilled under reduced pressure (bath temp 125 °C, 6 mm Hg). This afforded one fraction of I-17 as an oil, (25.04 g, 66%) bp 6 mm Hg, 78-82 °C.

INTERMEDIATE 18

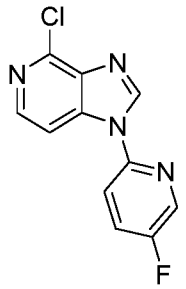
2-[4-[2,6-Dimethyl-4-(trifluoromethyl)anilino]imidazo[4,5-c]pyridin-1-yl]acetic acid



I-7 (389 mg, 2.05 mmol) and Cs_2CO_3 [534-17-8] (1.217 g, 3.735 mmol) were added to a solution of I-2 (500 mg, 1.87 mmol) in tBuOH [75-65-0] (31 mL) . Finally, BrettPhos [1470372-59-8] (102 mg, 0.11 mmol) was added and the mixture was heated at 100 °C for 16 h under a nitrogen atmosphere. After this time, the RM was concentrated under reduced pressure and the resulting residue was dissolved in water. The aq. solution was extracted with DCM (3x), then the combined OL was dried over $MgSO_4$, filtered and the solvents evaporated in vacuo. The resulting residue was purified by reverse phase (Phenomenex Gemini C18 100x30mm 5µm Column; from 81% [25mM NH_4HCO_3] - 19% [ACN:MeOH (1:1)] to 45% [25mM NH_4HCO_3] - 55% [ACN:MeOH (1:1)]). to yield 305 mg (44%) of Intermediate 18 as a white solid.

INTERMEDIATE 19

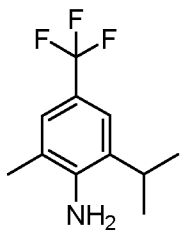
4-Chloro-1-(5-fluoropyridin-2-yl)-1H-imidazo[4,5-c]pyridine



K_2CO_3 (540 mg, 3.91 mmol) was added to a stirred solution of 4-chloro-1H-imidazo[4,5-c]pyridine [2770-01-6] (600 mg, 3.91 mmol) and 2,5-difluoropyridine [84476-99-3] (462 µL, 1.27 g/mL, 5.12 mmol) in DMF (9 mL) at RT. Then, the reaction mixture was stirred at 160 °C for 18 h. The mixture was cooled to RT and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 100/0). The desired fractions were collected and concentrated in vacuo to yield I-19 as a white solid (142 mg, 15%).

INTERMEDIATE 20

2-Isopropyl-6-methyl-4-(trifluoromethyl)aniline



2-Methyl-4-(trifluoromethyl)aniline [67169-22-6] (1 g, 5.71 mmol) was dissolved in DMF (20 mL). The reaction was cooled at 0°C. N-Bromosuccinimide (1.12 g, 6.28 mmol) was added. The mixture was warmed up to r.t. and stirred 16 hr at rt. EtOAc and sat. $NaHCO_3$ were added, the organic layer was separated, washed with water and dried over $MgSO_4$. The solution was filtered, and all volatiles were evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 20/80). The desired fractions were collected and concentrated in vacuo to yield 2-bromo-6-methyl-4-(trifluoromethyl)aniline as a brown viscous oil (1.38 g, 94%).

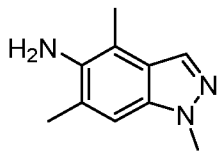
Cesium carbonate (2.15 g, 6.61 mmol) was added to a stirred solution of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane [95464-05-4]

(135 mg, 0.17 mmol) in water (2.5 mL) and 1,4-Dioxane (20 mL) previously degassed with nitrogen for 5 min. The mixture was stirred at rt for 5 min, then 2-bromo-6-methyl-4-(trifluoromethyl)aniline (700 mg, 2.76 mmol) and potassium trifluoro(prop-1-en-2-yl)borate [395083-14-4] (612 mg, 4.13 mmol) were sequentially added. The reaction mixture was stirred at 95 °C for 16h. The mixture was diluted with sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 10/90). The desired fractions were collected and concentrated in vacuo to yield 2-methyl-6-(prop-1-en-2-yl)-4-(trifluoromethyl)aniline as a yellow oil (416 mg, 95%)

Palladium on carbon (66 mg, 0.062 mmol) was added to a stirred solution of 2-methyl-6-(prop-1-en-2-yl)-4-(trifluoromethyl)aniline (416 mg, 1.93 mmol) in methanol (20 mL) at RT under nitrogen atmosphere. Then, nitrogen atmosphere was replaced by hydrogen and the reaction mixture was stirred at RT for 16h. The mixture was filtered over a pad of Celite® and was washed with MeOH/DCM mixture, then the solvents were removed in vacuo to yield 2-isopropyl-6-methyl-4-(trifluoromethyl)aniline as a brown oil (394 mg, 94%).

INTERMEDIATE 21

1,4,6-Trimethyl-1H-indazol-5-amine



Cesium carbonate (3.68 g, 11.29 mmol) and iodomethane (0.42 mL, 2.28 g/mL, 6.79 mmol) were added to a mixture of 6-methyl-5-nitro-1H-indazole [81115-43-7] (1 g, 5.64 mmol) in THF (25 mL) under nitrogen. The mixture was stirred at rt for 18 h. The solvent was evaporated in vacuo and the residue was dissolved in EtOAc and water. The organic layer was washed with water (x2) and brine, then separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 50/50). The desired fractions were collected and concentrated in vacuo to yield 1,6-dimethyl-5-nitro-1H-indazole as a yellow solid (573 mg, 53%).

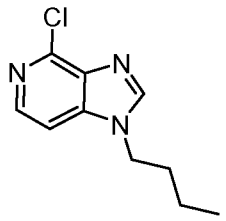
Pd/C (10%) (80 mg, 0.075 mmol) was added to a stirred solution of 1,6-dimethyl-5-nitro-1H-indazole (572 mg, 2.99 mmol) in MeOH (10 mL) under nitrogen. The mixture was hydrogenated at atmospheric pressure and RT for 18h. The mixture was filtered through a pad of Celite® and thefilter cake was washed with methanol. The filtrate was evaporated in vacuo to yield 1,6-dimethyl-1H-indazol-5-amine as a white solid (431, 89%).

1,6-Dimethyl-1H-indazol-5-amine (0.43 g, 2.67 mmol) was dissolved in DCM (20 mL). Then a Br_2 (0.15 mL, 3.12 g/mL, 2.94 mmol) solution in DCM (20 mL) was dropped into the solution under vigorous stirring. The mixture was stirred at room temperature for 16h. Then, DCM was added, and the solution was treated with water and the organic layer was dried with MgSO4. The solution was filtered, and all volatiles were evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 50/50). The desired fractions were collected and concentrated in vacuo to yield 4-bromo-1,6-dimethyl-1H-indazol-5-amine as a white solid (610 mg, 95%).

4-Bromo-1,6-dimethyl-1H-indazol-5-amine (610 mg, 2.54 mmol) and methylboronic acid [13061-96-6] (380 mg, 6.35 mmol) were added to a stirred solution of 1,4-dioxane (8 mL), water (2 mL), and sodium carbonate (808 mg, 7.62 mmol) under nitrogen. Then, $PdCl_2(dppf)_2$ [95464-05-4] (104 mg, 0.13 mmol) was added. The reaction mixture was stirred overnight at 105°C. Water and EtOAc were added. The organic layer was separated, dried ($MgSO_4$) and filtered and the solvents evaporated in vacuo. The crude was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 50/50). The desired fractions were collected and concentrated in vacuo to yield I-21 as a yellow solid (330 mg,74%).

INTERMEDIATE 22

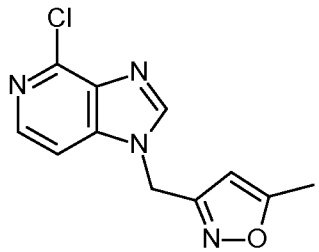
1-Butyl-4-chloro-1H-imidazo[4,5-c]pyridine [2137779-69-0]



4-Chloro-1H-imidazo[4,5-c]pyridine [2770-01-6] (500 mg, 3.26 mmol) was dissolved in DMF (7.6 mL) and sodium hydride (97.3 mg, 4.2 mmol) was added portionwise under nitrogen at 0° C. The RM was allowed to reach RT and stirring was continued for 45 min. Then, 1-bromobutane [109-65-9] (0.35 mL, 1.269 g/mL, 3.3 mmol) was added dropwise at 0 °C and the RM was allowed to reach RT and stirred overnight. $NaHCO_3$ sat solution was added and this was extracted with EtOAC, then washed with water and brine, then dried over $MgSO_4$ and solvent was removed in vacuo. The residue was purified by flash chromatography column (Heptane/EtOAc from 100/0 to 25/75) to obtain I-22 (300 mg, yield 43.945%) as a colourless oil.

INTERMEDIATE 23

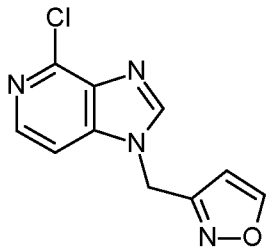
3-[(4-Chloroimidazo[4,5-c]pyridin-1-yl)methyl]-5-methyl-isoxazole



3-Chloromethyl-5-methylisoxazole [35166-37-1] (180 mg, 1.3 mmol) was added to a stirred solution of 4-Chloro-1H-imidazo[4,5-c]pyridine [2770-01-6] (200 mg, 1.24 mmol) and K_2CO_3 [584-08-7] (207 mg, 1.49 mmol) in acetonitrile [75-05-8] (4 mL) at RT. The RM was stirred at 75 °C for 16h. The mixture was diluted with sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was dried (MgSO4), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel using as eluent a gradient MeOH in DCM 0/100 to 3.5/96.5 to yield I-23 (85% purity, 64%) as a white foamy solid.

INTERMEDIATE 24

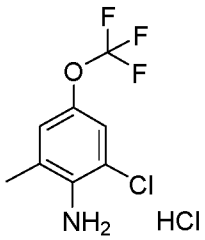
3-[(4-Chloroimidazo[4,5-c]pyridin-1-yl)methyl]isoxazole



Intermediate 24 was prepared in a similar manner to I-23, starting from 3-(chloromethyl)isoxazole [57684-71-6] and 4-chloro-1H-imidazo[4,5-c]pyridine [2770-01-6].

INTERMEDIATE 25

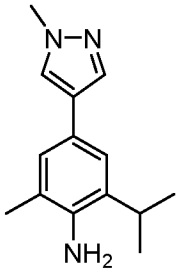
2-Chloro-6-methyl-4-(trifluoromethoxy)aniline hydrochloride



A pressure tube was charged with a solution of K_2CO_3 (7.14 g, 0.052 mol) in distilled water (7 mL), then dioxane (70 mL) was added. The suspension was purged with N_2 while adding 2-bromo-6-chloro-4-(trifluoromethoxy)aniline (5 g, 0.017 mol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(ii)dichloride dichloromethane complex (1.42 g, 0.0017 mol) and trimethylboroxine (2.67 mL, 0.019 mol). The tube was capped and placed in an oil bath of 120°C and the suspension was stirred for 16h at this temperature. The resulting suspension was treated with EtOAc/water to obtain a clear phase separation and the layers were separated. The aqueous layer was extracted with EtOAc (3x), and the combined OL were treated with brine, $MgSO_4$, filtered and concentrated in vacuo to afford an oil. This was pufied by silicagel chromatography using a 120 g Redisep flash column eluting with a gradient of 0-10% EtOAc in heptane to afford a colourless oil. This was dissolved in DIPE and treated with 6N HCl in iPrOH which after stirring for 16h at rt afforded a white solid which was collected by filtration to give I-25 (2.46 g, yield 55%).

INTERMEDIATE 26

2-Isopropyl-6-methyl-4-(1-methyl-1H-pyrazol-4-yl)aniline

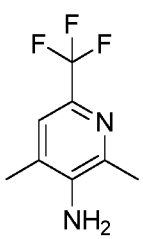


To 2-isopropyl-6-methylaniline [773887-07-3] (1 g, 6.701 mmol) in DMF(dry) (16 mL) at 0° was added NBS (1.30 g, 7.4 mmol). The reaction mixture was then allowed to warm to RT and stirred overnight. Water was then added to the r.m. and it was extracted with DCM. The organic layer was dried over $MgSO_4$ and coevaporated with MIK. The crude was then purified with using pure heptane to 20% of EtOAc as eluent. All product fractions were pooled and evaporated to give 4-bromo-2-isopropyl-6-methylaniline (1.30 g, yield 85%).

A solution of 4-bromo-2-isopropyl-6-methylaniline (871 mg, 3.82 mmol), 1-methyl-1H-pyrazole-4-boronic acid (744 mg, 4.58 mmol) and sodium carbonate (1.2 g, 11 mmol) in a mixture of 1,4-dioxane (16 mL) and water (0.1 mL) was bubbled with N_2 for 5 minutes. Then $PdCl_2(dppf)_2$ [95464-05-4] (156 mg, 0.191 mmol) was added and the reaction mixture was stirred for 6 hours at 100°C. Water and EtOAc were added and the layers were separated, the organic layer was dried over $MgSO_4$ and evaporated. Purification by column chromatography was performed using pure heptane to 50% EtOAc in heptane. Desired fractions were combined and the solvents evaporated to yield I-26 (855 mg, yield 98%).

INTERMEDIATE 27

2,4-Dimethyl-6-(trifluoromethyl)pyridin-3-amine



This reaction was performed in two microwave vials:

1. 2,4-dibromo-6-(trifluoromethyl)pyridin-3-amine [1214365-67-9] (900 mg, 2.813 mmol) was dissolved in a mixture of 1,4-dioxane (7.2 mL) and water (0.9mL). trimethylboroxine [823-96-1] (1.13 mL, 0.896 g/mL, 8.07 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex [95464-05-4] (206 mg, 0.252 mmol) and K_2CO_3 (1.2 g, 8.5 mmol) were added to the solution and the mixture was heated at 140° for 1 h using a microwave. Water and EtOAc were added to the mixture and the aqueous layer was extracted. It was then washed with brine, dried over $MgSO_4$ and the solvent evaporated.

2. 2,4-dibromo-6-(trifluoromethyl)pyridin-3-amine [1214365-67-9] (100 mg, 0.313 mmol) was disolved in a mixture of 1,4-dioxane (0.8 mL) and water (0.1mL). trimethylboroxine [823-96-1] (0.126 mL, 0.896 g/mL, 0.896 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex [95464-05-4] (23 mg, 0.028 mmol) and K_2CO_3 (0.13 g, 0.94 mmol) were added to the solution and the mixture was heated at 140° for 1 hr using a microwave. Both crude r.m. were combined and purified with FCC with pure DCM as eluent. All product fractions were combined and evaporated to yield I-27 (424 mg, yield 79%).

INTERMEDIATE 28

4-(Difluoromethyl)-2-methylpyridin-3-amine

Lithium aluminium hydride [16853-85-3] (0.2 g, 5.14 mmol) was added to a stirred solution of methyl 3-amino-2-chloroisonicotinate [173435-41-1] (1 g, 4.29 mmol) in dry THF (10 mL) at -20 °C. The mixture was stirred at 0°C for 30 min. NH_4Cl (800 mg), MeOH (5 mL) and $MgSO_4$ were added and the mixture was stirred 15 min. The mixture was filtered and concentrated in vacuo. The crude was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 3.5/96.5). The desired fractions were collected and concentrated in vacuo to yield (3-amino-2-chloropyridin-4-yl)methanol as a white solid (704 mg, 100%).

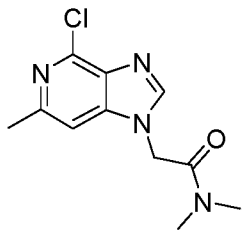
Dess-Martin periodinane [87413-09-0] (2.82 g, 6.66 mmol) was added to a stirred

solution of (3-amino-2-chloropyridin-4-yl)methanol (704 mg, 4.44 mmol) in THF (44 mL) and DCM (44 mL). Then, the mixture was quenched with saturated $NaHCO_3$ solution and $Na_2S_2O_3$ (1.5 g) and EtOAc (45 mL). The mixture was stirred for 30 min and then diluted with EtOAc (20 mL). The organic layer was separated, washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield 3-amino-2-chloroisonicotinaldehyde as a yellow solid (480 mg, 68%).

DAST [38078-09-0] (1.71 mL, 1.22 g/mL, 12.3 mmol) was added to a solution of 3-amino-2-chloroisonicotinaldehyde (480 mg, 3.07 mmol) in anhydrous DCM (30 mL) at -78 °C under nitrogen. The reaction was strirred from -78°C to rt for 48 h. The reaction was diluted with sat. $NaHCO_3$ at 0°C and extracted with EtOAc. The organic layer was separated, dried (MgSO4), filtered and the solvents were evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 12/88) to yield I-28 as an orange solid (170 mg, 30%).

INTERMEDIATE 29

2-(4-Chloro-6-methyl-1H-imidazo[4,5-c]pyridin-1-yl)-N,N-dimethylacetamide



4-Hydroxy-6-methyl-3-nitropyridin-2(1H)-one [4966-90-9] (5 g, 29 mmol) in $POCl_3$ (20 mL, 1.65 g/mL, 215 mmol) was stirred at 100 °C for 2h. The mixture was cooled at rt, then was concentrated in vacuo and co-evaporated with toluene. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 20/80). The desired fractions were collected and concentrated in vacuo to yield 2,4-dichloro-6-methyl-3-nitropyridine as a white solid (2.77 g, 45%).

Ammonia solution, 7 N in methanol [7664-41-7] (14.1 mL, 7 M, 98.59 mmol) was added to a stirred solution of 2,4-dichloro-6-methyl-3-nitropyridine (2.77 g, 13.4 mmol) in THF (28 mL). The solvent was evaporated in vacuo and the mixture was purified by flash

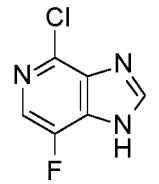
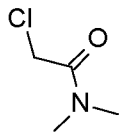
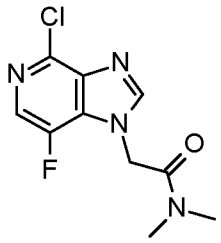
column chromatography (silica; EtOAc in heptane 0/100 to 20/80). The desired fractions were collected and concentrated in vacuo to yield 2-chloro-6-methyl-3-nitropyridin-4-amine as a yellow solid (1.0 g, 36%).

Iron powder [7439-89-6] (1.52 g, 27.2 mmol) was added to a solution of 2-chloro-6-methyl-3-nitropyridin-4-amine (1 g, 5.3 mmol), ammonium chloride (2.42 g, 27.2 mmol) and water (4.8 mL) in ethanol (18.5 mL). The mixture was allowed to cool to RT the mixture was filtered through celite®. The solvent was evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, Eluent: DCM/MeOH 100/0 to 95/5). The desired fractions were collected and concentrated to yield 2-chloro-6-methylpyridine-3,4-diamine as a brown solid (410 mg, 44%).

A mixture of 2-chloro-6-methylpyridine-3,4-diamine (360 mg, 2.28 mmol), triethyl orthoformate [122-51-0] (2.2 mL, 0.89 g/mL, 13 mmol) and acetic anhydride [108-24-7] (2.2 mL, 1.08 g/mL, 23 mmol) was stirred at 140 °C for 5h. The excess reagents were removed by evaporation. Then the mixture was treated with water, and NaOH (10%) was added until pH 9 at 0°C. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, DCM/MeOH 100/0 to 95/5). The desired fractions were collected and concentrated to yield 4-chloro-6-methyl-1H-imidazo[4,5-c]pyridine as a white solid (306 mg, 70%).

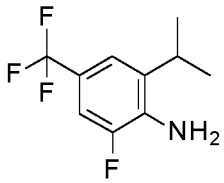
Potassium carbonate (577 mg, 2.51 mmol) was added to a mixture 4-chloro-6-methyl-1H-imidazo[4,5-c]pyridine (350 mg, 2.09 mmol) in acetonitrile (8.0 mL) at r.t. under a nitrogen atmosphere. Then 2-chloro-N,N-dimethylacetamide [2675-89-0] (226 µL, 1.18 g/mL, 2.2 mmol) in acetonitrile (8 mL) was added dropwise and the mixture was stirred at 70°C for 16 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water (x2) and brine, then separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude was purified by flash column chromatography (silica, EtOAc in heptane 0/100 to 80/20) to yield I-29 as a white sticky solid (307 mg, 58%).

The following Intermediates were prepared in a similar manner.

Starting material	Reagent	Compound
 [405230-97-9]	 [2675-89-0]	 I-30

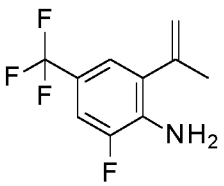
INTERMEDIATE 31

2-Fluoro-6-isopropyl-4-(trifluoromethyl)aniline



Step 1.

2-Fluoro-6-isopropenyl-4-(trifluoromethyl)aniline



Cesium carbonate [534-17-8] (1.712 g, 5.256 mmol) was added to a stirred solution of [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane [95464-05-4] (107.563 mg, 0.131 mmol) in a previously degassed solution of water (2.01 mL) and 1,4-dioxane (16.0 mL). The mixture was stirred at rt for 5 min, then 2-bromo-6-fluoro-4-(trifluoromethyl)aniline [1034325-63-7] (565 mg, 2.19 mmol) and potassium trifluoro(prop-1-en-2-yl)borate [395083-14-4] (486 mg, 3.28 mmol) were sequentially added. The reaction mixture was stirred at 95 °C for 16 h, when analysis by TLC indicated complete conversion. The rm was diluted with sat. aq. $NaHCO_3$ soln. and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 10/90). The desired fractions were collected and

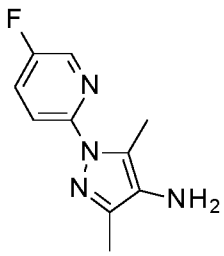
concentrated in vacuo to yield 217 mg (44.76%) of 2-fluoro-6-isopropenyl-4-(trifluoromethyl)aniline.

Step 2.

Palladium on carbon [7440-05-3] (33.4 mg, 0.031 mmol) was added to a stirred solution of 2-fluoro-6-isopropenyl-4-(trifluoromethyl)aniline (215 mg, 0.98 mmol) in methanol (10 mL) at rt under nitrogen atomosphere. Then, nitrogen atmosphere was replaced by hydrogen and the rm was stirred at rt for 16 h . The mixture was filtered over a pad of celite®, washed with a mixture of MeOH/DCM, and the solvents removed in vacuo to yield 168 mg (73.6 %) of I-31 as an orange oil.

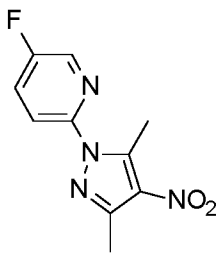
INTERMEDIATE 32

1-(5-Fluoro-2-pyridyl)-3,5-dimethyl-pyrazol-4-amine



Step 1.

2-(3,5-dimethyl-4-nitro-pyrazol-1-yl)-5-fluoro-pyridine



3,5-Dimethyl-4-nitro-1h-pyrazole [14531-55-6] (600 mg, 4.25 mmol), 2-bromo-5-fluoropyridine [41404-58-4] (1.53 g, 8.50 mmol) and K_2CO_3 [584-08-7] (1. 24 g, 8.93 mmol) were dissolved in previously degassed DMA (3 mL) in a sealed tube under nitrogen. Then copper iodide [7681-65-4] (41 mg, 0.21 mmol) and N,N'-dimethylcyclohexane-1,2-diamine [61798-24-1] (138 µL, 0.902 g/mL, 0.85 mmol) were added and the resulting mixture was stirred at 180 °C for 4 h. The rm was diluted with sat. aq $NaHCO_3$ soln and extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and the solvents evaporated in vacuo. The resulting residue

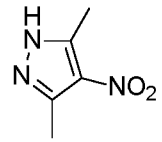
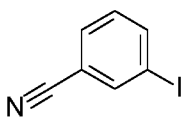
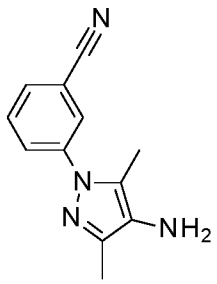
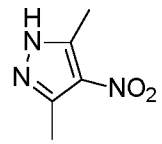
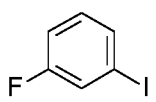
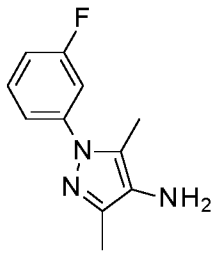
was purified by flash column chromatography on silica gel, using as eluent a gradient EtOAc/heptane, 0/100 to 20/80, to yield 146 mg (14%) of 2-(3,5-dimethyl-4-nitro-pyrazol-1-yl)-5-fluoro-pyridine as a yellow solid.

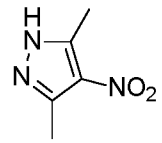
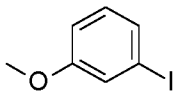
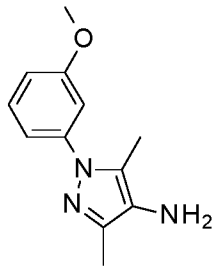
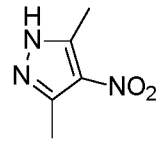
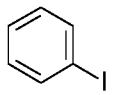
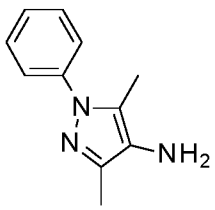
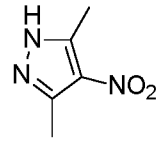
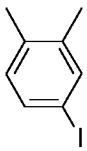
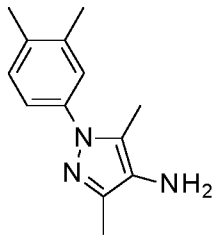
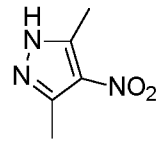
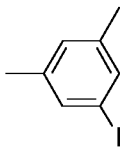
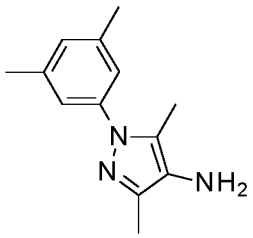
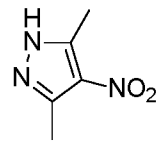
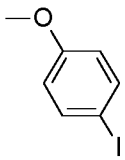
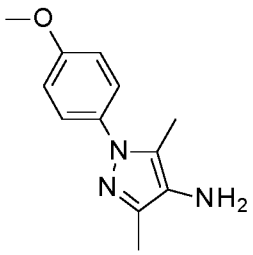
Step 2.

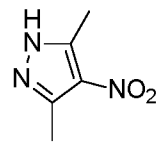
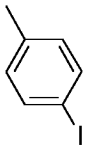
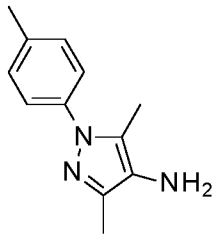
1-(5-Fluoro-2-pyridyl)-3,5-dimethyl-pyrazol-4-amine

Iron [7439-89-6] (0.17 g, 3.09 mmol) was added to a stirred suspension of 2-(3,5-dimethyl-4-nitro-pyrazol-1-yl)-5-fluoro-pyridine (146 mg, 0.62 mmol) and NH_4Cl [12125-02-9] (132 mg, 2.47 mmol) in a mixture of ethanol (4 mL) and water (0.62 mL). The mixture was stirred at 65 °C for 3 h, then it was filtered over a pad of celite®, washed with MeOH/DCM mixture, then the solvents were removed in vacuo. The resulting residue was diluted with $NaHCO_3$ and was extracted with a mixture of $CHCl_3$/MeOH (4:1). The organic layer was dried over $MgSO_4$, filtered and the solvents evaporated in vacuo to yield I-32 (106 mg, 82%) as a yellow oil.

The following Intermediates were prepared in a similar manner:

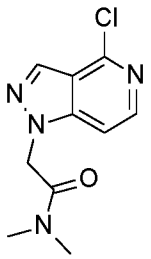
Starting material	Reagent	Compound
 [14531-55-6]	 [69113-59-3]	 I-33
 [14531-55-6]	 [1121-86-4]	 I-34

Starting material	Reagent	Compound
 [14531-55-6]	 [766-85-8]	 I-35
 [14531-55-6]	 [591-50-4]	 I-36
 [14531-55-6]	 [31599-61-8]	 I-37
 [14531-55-6]	 [22445-41-6]	 I-38
 [14531-55-6]	 [696-62-8]	 I-39

Starting material	Reagent	Compound
 [14531-55-6]	 [31599-61-8]	 I-40

INTERMEDIATE 41

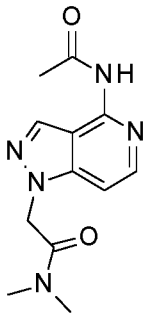
2-(4-Chloropyrazolo[4,3-c]pyridin-1-yl)-N,N-dimethyl-acetamide



To a mixture of 4-chloro-1*H*-pyrazolo[4,3-*c*]pyridine [871836-51-0] (846 mg, 5.51 mmol) in DMF, NaH [7646-69-7] (331 mg, 8.26 mmol) was added portionwise at RT and under a nitrogen atmosphere (15 mL) over 1 min. The RM was stirred at RT for 1 h, then 2-chloro-N,N-dimethylacetamide [2675-89-0] (0.68 mL, 1.182 g/mL, 6.61 mmol) was added dropwise and the resulting mixture was stirred at RT for 2.5 h. The solvent was evaporated in vacuo and the resulting residue was partitioned between EtOAc and water. The organic layer was separated, then washed with water (x2) and brine, dried over $MgSO_4$, filtered and the solvents evaporated in vacuo. The resulting residue was purified by flash column chromatography on silica gel using as eluent a gradient EtOAc/heptane, 0/100 to 20/80, to yield I-41 (566 mg, 43%) as a white solid.

INTERMEDIATE 42

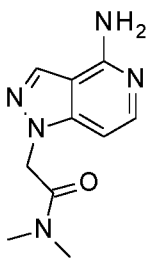
2-(4-Acetamidopyrazolo[4,3-c]pyridin-1-yl)-N,N-dimethyl-acetamide



Acetamide [60-35-5] (123 mg, 2.07 mmol) and I-17 (450 mg, 1.88 mmol) were added to a stirred solution of palladium(II) acetate [3375-31-3] (17.0 mg, 0.075 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene [161265-03-8] (98.2 mg, 0.17 mmol) and cesium carbonate [534-17-8] (1.23 g, 3.77 mmol) in anhydrous dioxane (10 mL) under nitrogen. The resulting mixture was stirred and heated at 90 ºC for 18 h, then it was concentrated under reduced pressure. The resulting residue was partitioned between EtOAc and water. The organic layer was separated, washed with water, dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by flash column chromatography on silica gel, using as eluent a gradient DCM/MeOH (9:1) in DCM, 0/100 to 100/0, to yield I-42 (390 mg, 79%) as a yellow solid.

INTERMEDIATE 43

2-(4-Aminopyrazolo[4,3-c]pyridin-1-yl)-N,N-dimethyl-acetamide

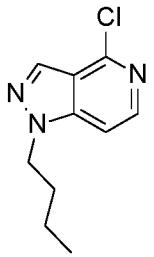


A solution of hydrochloric acid in methanol [132228-87-6] (3.6 mL, 1.25 M, 4.48 mmol) was added to a solution of I-18 (390 mg, 1.49 mmol) in MeOH (2 mL) and the mixture was stirred at 80 ºC for 18 h. Another portion of hydrochloric acid in methanol [132228-87-6] (1.2 mL, 1.25 M, 1.49 mmol) was added to the RM, which was stirred and heated at 80 ºC for 48 h. After this time the solvents were evaporated in vacuo and the resulting residue was partitioned between $NaHCO_3$ and EtOAc. The Ol was

separated, and the aqueous back extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo to yield I-43 (431 mg, 97%) as a yellow solid.

INTERMEDIATE 44

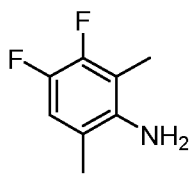
1-Butyl-4-chloro-pyrazolo[4,3-c]pyridine



To a solution of 4-chloro-1H-pyrazolo[4,3-c]pyridine [871836-51-0] (100 mg, 0.65 mmol) in anhydrous DMF (4.0 mL) was added NaH (60% dispersion in mineral oil) [7646-69-7] (26.0 mg, 0.65 mmol) at RT. When the gas evolution stopped, 1-bromobutane [109-65-9] (70 µL, 1.276 g/mL, 0.65 mmol) was added at RT. The RM was stirred at RT for 3 h, then it was quenched with water and EtOAc was added. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, using as eluent a gradient heptane/EtOAc, 100/0 to 90/10, to afford I-44 (50 mg 36.6%) as an oil, and its regioisomer, 2-butyl-4-chloro-pyrazolo[4,3-c]pyridine (28 mg, 20.5%) as an oil.

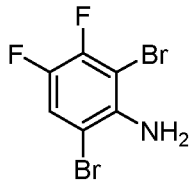
INTERMEDIATE 45

3,4-Difluoro-2,6-dimethylaniline



Step 1.

2,6-Dibromo-3,4-difluoroaniline



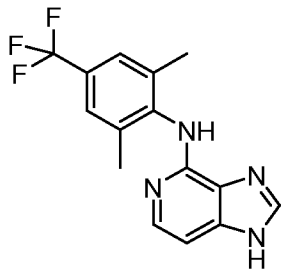
N-Bromosuccinimide [128-08-5] (16.2 g, 91.02 mmol) was added to a stirred solution of 3,4-difluoroaniline [3863-11-4] (3.84 mL, 38.73 mmol) in acetonitrile (100 mL). The mixture was stirred at 86 °C for 16 h. The mixture was concentrated in vacuo and the residue was residue was purified by flash column chromatography on silica gel, using as eluent a gradient EtOAc/heptane, 5/95 to 20/80. The desired fractions were collected and concentrated in vacuo to afford 2,6-dibromo-3,4-difluoroaniline (9 g, 79%) as a brown solid.

Step 2.

Pd_2dba_3 [51364-51-3] (160 mg, 0.17 mmol), X-Phos [564483-18-7] (166 mg, 0.35 mmol) and tripotassium phosphate [7778-53-2] (2.22 g, 10.46 mmol) were diluted in 1,4-dioxane (35 mL, presiously degassed bubbling nitrogen for 5 minutes) in a sealed tube under nitrogen atmosphere. Then, 2,6-dibromo-3,4-difluoroaniline (1 g, 3.49 mmol) and trimethylboroxine [823-96-1] (1.46 mL, 0.9 g/mL, 10.46 mmol) were added and the mixture was stirred at 100 °C for 18 h. The mixture was filtrated over Celite® and washed with a mixture of DCM/MeOH (9:1). The solvents were concentrated in vacuo and the residue was residue was purified by flash column chromatography on silica gel (dried load), using as eluent a gradient EtOAc/heptane, 0/100 to 30/70, to afford two fractions of I-45: fraction 1 (700 mg, 64%) and fraction 2 (79 mg, 14%) both as red oils. Fraction 1 was repurified by flash column chromatography on silica gel, using as eluent a gradient EtOAc/heptane, 0/100 to 30/70, to afford a third fraction of I-45 (288 mg, 52%) as red oil

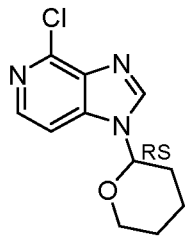
INTERMEDIATE 46

N-(2,6-Dimethyl-4-(trifluoromethyl)phenyl)-1H-imidazo[4,5-c]pyridine-4-amine pyridine



Step 1.

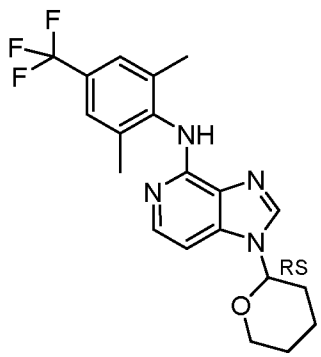
Rac-4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-imidazo[4,5-c]pyridine pyridine



3,4-Dihydro-2H-pyran [110-87-2] (2.38 mL, 26.05 mmol) and p-toluenesulfonic acid monohydrate [6192-52-5] (0.25 g, 1.30 mmol) were added to a stirred solution of 4-chloro-1H-imidazo[4,5-c]pyridine [2770-01-6] (2 g, 13.02 mmol) in DCM (60 mL). The mixture was stirred at 40 °C for 48 h. The mixture was diluted with sat. $NaHCO_3$ and extracted with DCM (x 2). The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel, using as eluent a gradient EtOAc/heptane, 0/100 to 100/0. The desired fractions were collected and concentrated in vacuo to yield rac-4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-imidazo[4,5-c]pyridine (2.5 g, 79%) as a colourless oil.

Step 2.

N-(2,6-dimethyl-4-(trifluoromethyl)phenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-imidazo[4,5-c]pyridine-4-amine



A mixture of rac-4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-imidazo[4,5-c]pyridine (1 g, 4.21 mmol), I-27 (0.876 g, 4.63 mmol) and Cs_2CO_3 [534-17-8] (3.02 g, 9.26 mmol) in DMA (16 mL) was degassed with nitrogen. $Pd(OAc)_2$ [3375-31-3] (189 mg, 0.84 mmol) and Xantphos [161265-03-8] (487 mg, 0.84 mmol) were added and the mixture was heated at 130°C for 16h. The mixture was concentrated under reduced pressure. The residue was diluted with water, extracted with DCM, dried on $MgSO_4$, filtered and the solvents evaporated in vacuo. The crude product was purified by flash column

chromatography on silica gel, using as eluent a gradient EtOAc/heptane, 0/100 to 80/20. The desired fractions were collected and concentrated in vacuo to yield N-(2,6-dimethyl-4-(trifluoromethyl)phenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-imidazo[4,5-c]pyridine-4-amine(906 mg, 55%) as a yellow foam.

Step 3

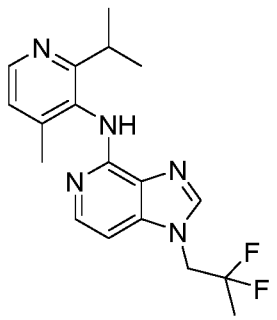
N-(2,6-Dimethyl-4-(trifluoromethyl)phenyl)-1H-imidazo[4,5-c]pyridine-4-amine pyridine

TFA [76-05-1] (5.91 mL, 76.58 mmol) was added to a stirred solution of N-(2,6-dimethyl-4-(trifluoromethyl)phenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-imidazo[4,5-c]pyridine-4-amine(906 mg, 2.32 mmol). The reaction mixture was stirred at rt for 1.5 h. The solvent was evaporated in vacuo. The mixture was diluted with sat. $NaHCO_3$ and extracted with DCM. The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo to yield I-46 (495 mg, 70%) as a yellow solid which was used in the next reaction step without further purification.

PREPARATION OF FINAL COMPOUNDS

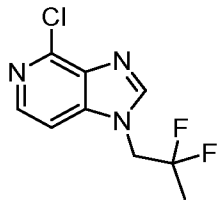
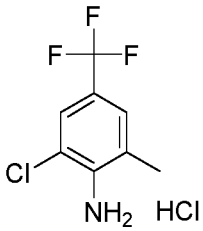
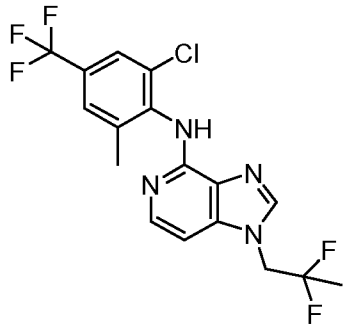
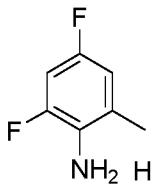
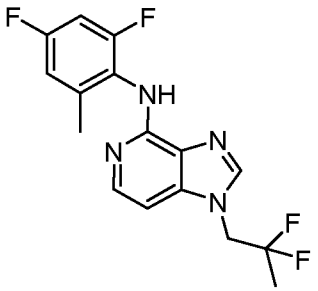
COMPOUND 1

1-(2,2-Difluoropropyl)-N-(2-isopropyl-4-methylpyridin-3-yl)-1H-imidazo[4,5-c]pyridin-4-amine



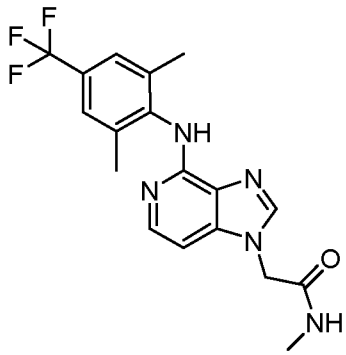
A mixture of I-13 (200 mg, 0.863 mmol), I-15 (160 mg, 1.07 mmol) and Cs_2CO_3 (563 mg, 1.73 mmol) in tBuOH (2.4 mL) was degassed with N_2. $Pd(OAc)_2$ (36 mg, 0.16 mmol) and Xantphos [161265-03-8] (60.5 mg, 0.104 mmol) were added and the mixture was heated for 1h at 110°C. The mixture was diluted in DCM and filtrated over Celite® and the solvents were concentrated in vacuo. The product was purified on silica gel, eluent: 0-5% 7M NH_3/MeOH in DCM. The desired fractions were evaporated and crystallized from DIPE. The crystals were filtered off and dried to yield Co. No. 1 as a white solid (139 mg, 47%).

The following compounds were synthesized in an analogous manner from the indicated Intermediates and reagents

Starting material	Reagent	Compound
 I-13	 I-14	 Co. No. 2
Intermediate 3	 [1464825-76-0]	 Co. No. 3

COMPOUND 4

2-(4-((2,6-Dimethyl-4-(trifluoromethyl)phenyl)amino)-1H-imidazo[4,5-c]pyridin-1-yl)-N-methylacetamide



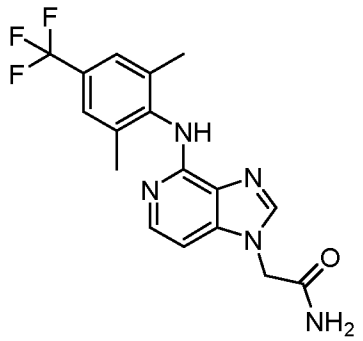
I-2 (389 mg, 2.05 mmol) and Cs_2CO_3 (1.22 g, 3.74 mmol) were added to a solution of Intermediate 8 (500 mg, 1.87 mmol) and tBuOH (31 mL). Then, BrettPhos [1470372-59-8] (102 mg, 0.11 mmol) was added and the mixture was heated at 100°C for 16 hours under a nitrogen atmosphere. The mixture was concentrated under reduced pressure,

taken up in water, extracted with DCM, dried on $MgSO_4$, filtered and the solvents evaporated in vacuo. The crude was purified by reverse phase (Phenomenex Gemini C18 100x30mm 5µm Column; from 81% [25mM NH_4HCO_3] - 19% [ACN:MeOH (1:1)] to 45% [25mM NH_4HCO_3] - 55% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated to yield 2-(4-((2,6-dimethyl-4-(trifluoromethyl)phenyl)amino)-1H-imidazo[4,5-c]pyridin-1-yl)acetic acid as a white solid (305 mg, 44%).

N-Methylimidazole [616-47-7] (36 µL, 0.74 g/mL, 0.33 mmol) was added to a stirred solution of 2-(4-((2,6-dimethyl-4-(trifluoromethyl)phenyl)amino)-1H-imidazo[4,5-c]pyridin-1-yl)acetic acid (70 mg, 0.19 mmol) and methylamine hydrochloride [593-51-1] (19.5 mg, 0.29 mmol) in NMP (1.18 mL) and ACN (0.59 mL) at rt. The reaction was heated at 65°C for 15 min until homogeneous solution. HOBt [123333-53-9] (39 mg, 0.29 mmol) and EDC-HCl [25952-53-8] (53 mg, 0.27 mmol) were added at RT The mixture was stirred at 65°C for 1.5 h and then at rt for 16h. The mixture was diluted with sat. $NaHCO_3$ at 0°C and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; 0-10% MeOH in DCM). The desired fractions were collected and concentrated in vacuo. The product was triturated with DIPE to yield Co. No. 4 as a white solid (62.5, 85%).

COMPOUND 5

2-[4-[2,6-Dimethyl-4-(trifluoromethyl)anilino]imidazo[4,5-c]pyridin-1-yl]acetamide

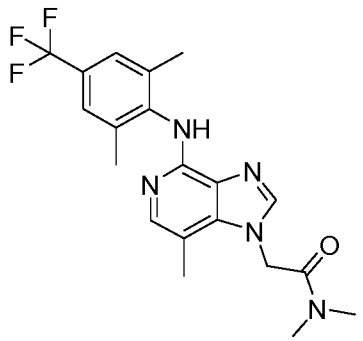


N-Methylimidazole [616-47-7] (43.07 µL, 0.742 g/mL, 0.387 mmol) was added to a stirred solution of I-18 (83 mg, 0.228 mmol) and NH_3 [7664-41-7] (0.5 M in dioxane, 683.461 µL 0.342 mmol) in a mixture of NMP [872-50-4] (1.4 mL) and ACN (0.698 mL) at rt. The reaction was heated at 65 °C for 15 min until homogeneus solution.

HOBt [123333-53-9] (46.176 mg, 0.342 mmol) and EDC-HCl [25952-53-8] (63.034 mg, 0.319 mmol) were added at r.t. The mixture was stirred at 65°C for 1.5 h. The mixture was diluted with sat. $NaHCO_3$ at 0 °C and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 10/90). The crude was purified by reverse phase (Phenomenex Gemini C18 100x30mm 5µm Column; from 72% [25mM NH_4HCO_3] - 28% [ACN:MeOH (1:1)] to 36% [25mM NH_4HCO_3] - 64% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated in vacuo. The product was tritured with DIPE to yield Co. No. 5 as a white solid.

COMPOUND 6

2-(4-((2,6-Dimethyl-4-(trifluoromethyl)phenyl)amino)-7-methyl-1H-imidazo[4,5-c]pyridin-1-yl)-N,N-dimethylacetamide

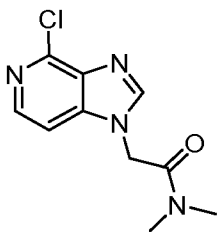
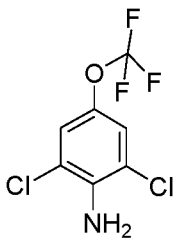
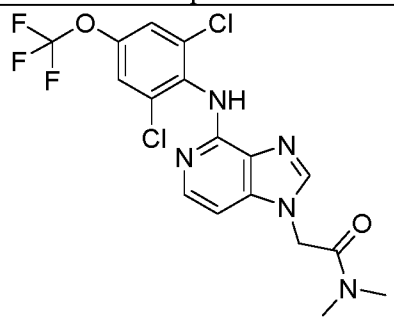
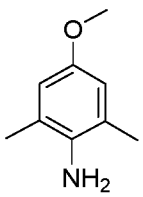
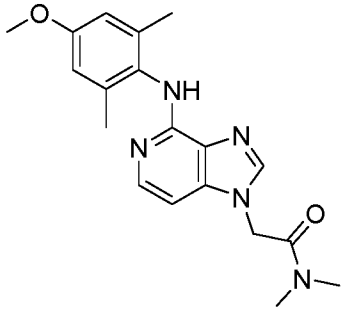


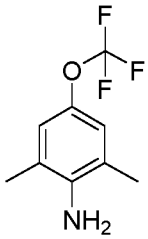
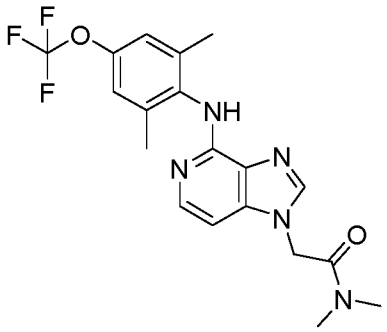
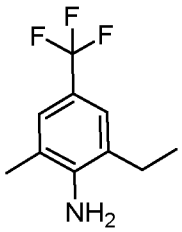
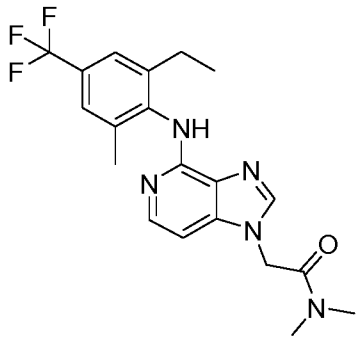
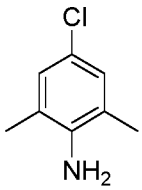
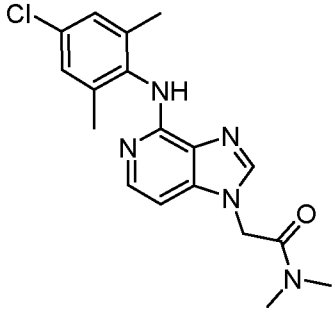
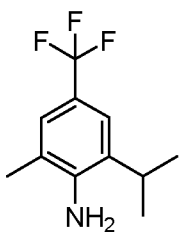
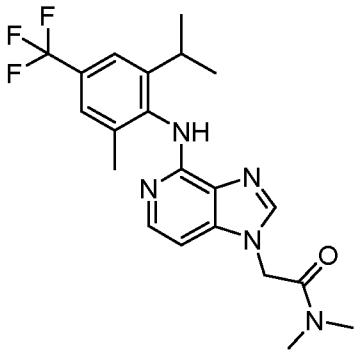
N-iodosuccinimide (95 mg, 0.42 mmol) was added portionwise to a solution of compound 61 (150 mg, 0.38 mmol) in DMF (1.5 mL). The reaction mixture was stirred at room temperature 16 h. The mixture was diluted with sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 30/70). The desired fractions were collected and concentrated in vacuo to yield 2-(4-((2,6-dimethyl-4-(trifluoromethyl)phenyl)amino)-7-iodo-1H-imidazo[4,5-c]pyridin-1-yl)-N,N-dimethylacetamide as a white solid (172 mg, 82%).

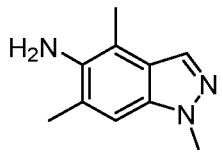
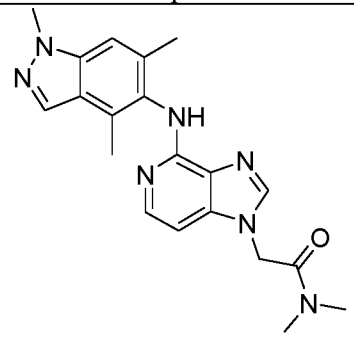
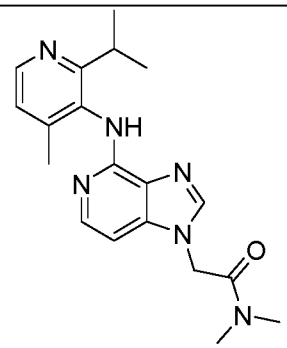
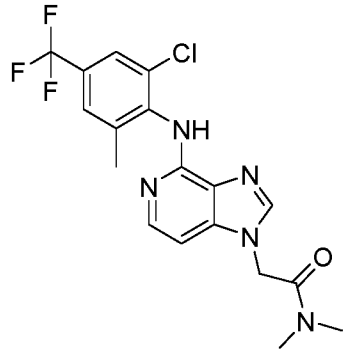
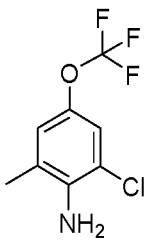
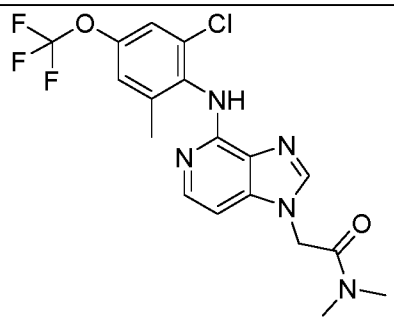
Trimethylboroxine [823-96-1] (69 µL, 0.9 g/mL, 0.49 mmol) was added to a stirred suspension of 2-(4-((2,6-dimethyl-4-(trifluoromethyl)phenyl)amino)-7-iodo-1H-imidazo[4,5-c]pyridin-1-yl)-N,N-dimethylacetamide (170 mg, 0.33 mmol), K_3PO_4 (140

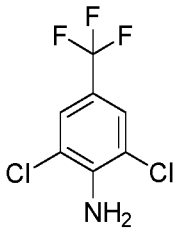
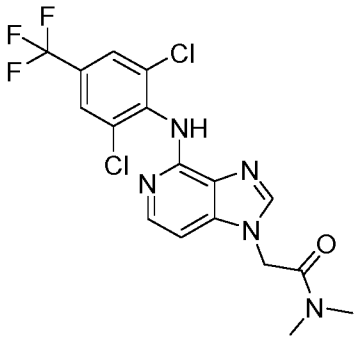
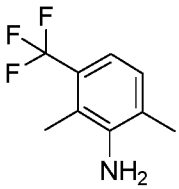
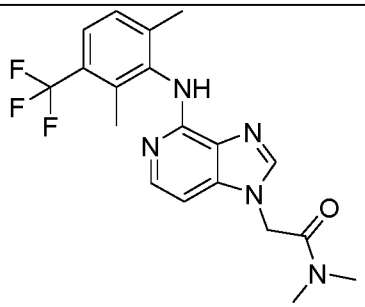
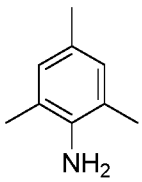
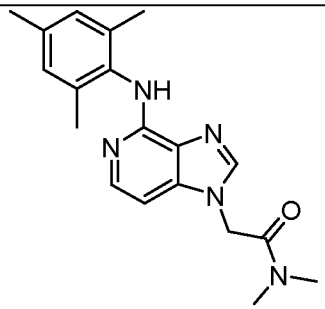
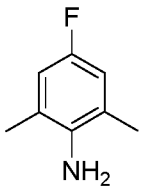
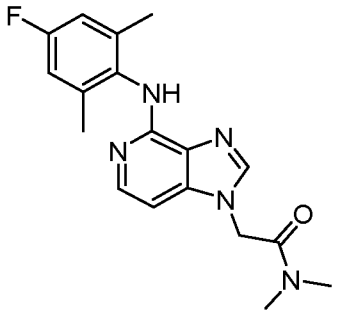
mg, 0.66 mmol), X-Phos [564483-18-7] (16 mg, 0.033 mmol) and $Pd_2(dba)_3$ [51364-51-3] (15.05 mg, 0.016 mmol) in 1,4-dioxane (3 mL) under nitrogen. The mixture was stirred at 95 °C 16 h. The same amounts of trimethylboroxine [823-96-1] (69 µL, 0.9 g/mL, 0.49 mmol), 2-(4-((2,6-dimethyl-4-(trifluoromethyl)phenyl)amino)-7-iodo-1H-imidazo[4,5-c]pyridin-1-yl)-N,N-dimethylacetamide (170 mg, 0.33 mmol), X-Phos [564483-18-7] (16 mg, 0.033 mmol) and $Pd_2(dba)_3$ [51364-51-3] (15.05 mg, 0.016 mmol) were added. The reaction was stirred at 110°C for another 16 h. Water and EtOAc were added. The organic layer was separated, dried ($MgSO_4$) and filtered and the solvents evaporated in vacuo. The crude was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 50/50). The desired fractions were collected and concentrated in vacuo to yield a pale-yellow sticky solid. The crude was purified by reverse phase (Phenomenex Gemini C18 100x30mm 5µm Column; from 72% [25mM NH_4HCO_3] - 28% [ACN:MeOH (1:1)] to 36% [25mM NH_4HCO_3] - 64% [ACN:MeOH (1:1)]), to yield Co. No. 6 after trituration with DIPE as an off white solid (22 mg, 16%).

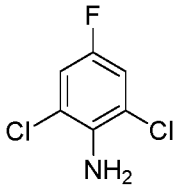
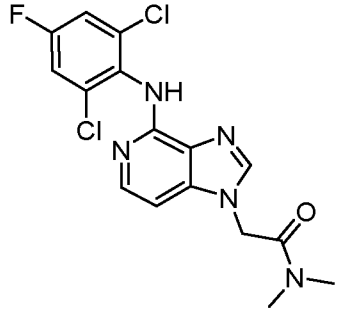
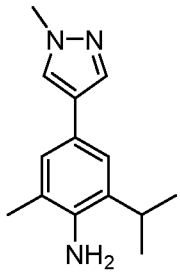
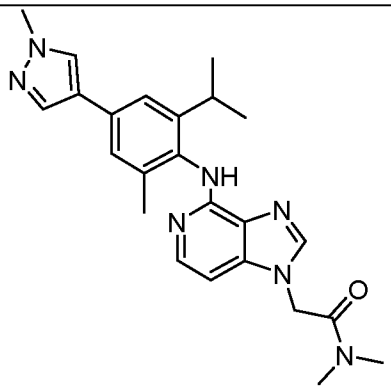
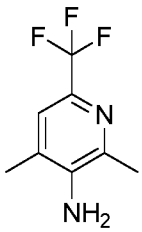
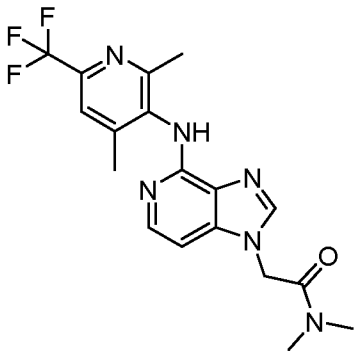
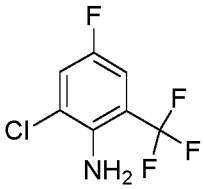
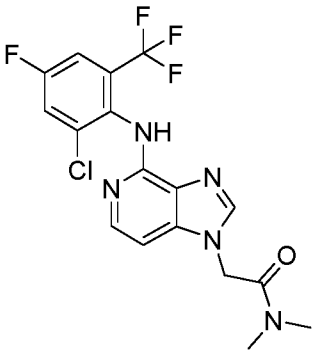
The following compounds were synthesized in an analogous manner from the indicated Intermediates and reagents

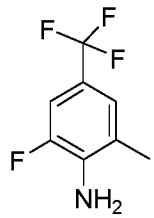
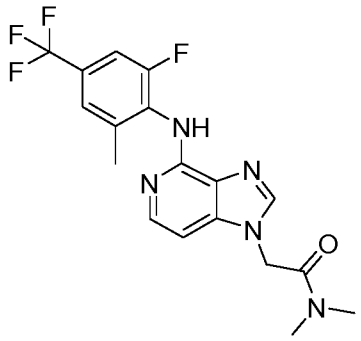
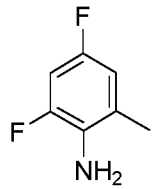
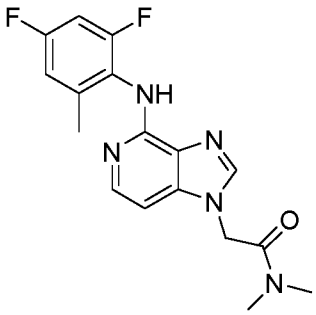
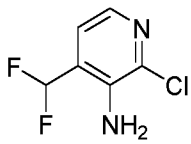
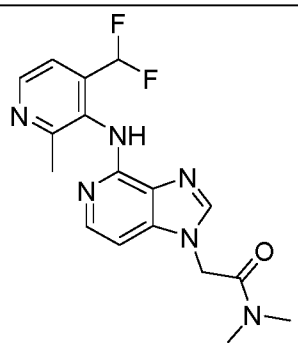
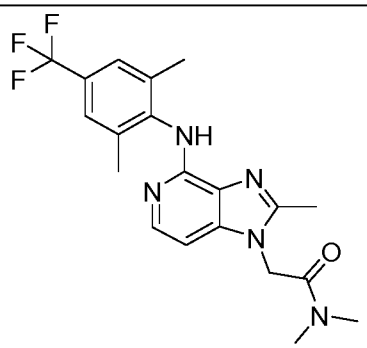
Starting material	Reagent	Compound
 I-1	 [99479-66-0]	 Co. No. 7
I-1	 [34743-49-2]	 Co. No. 8

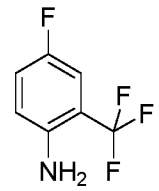
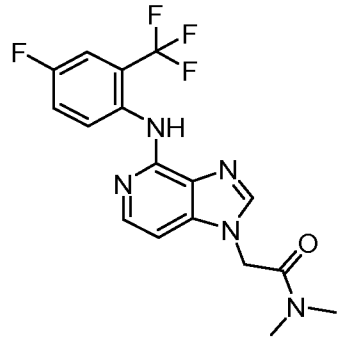
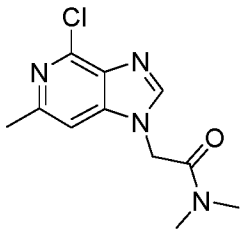
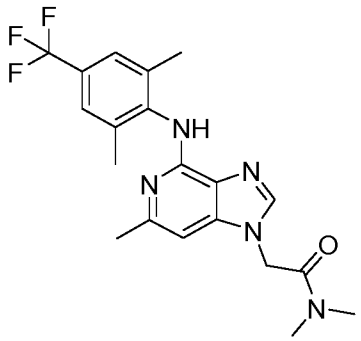
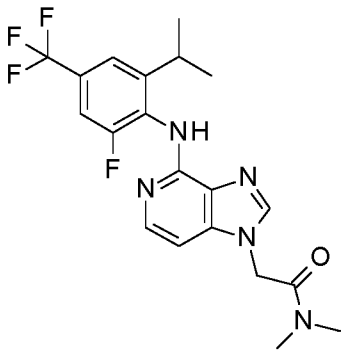
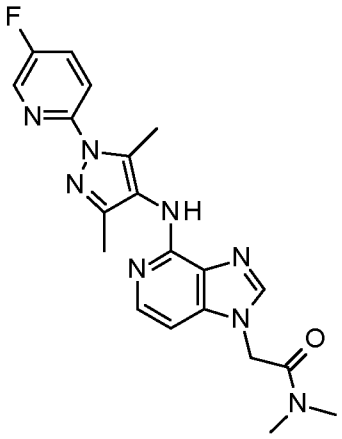
Starting material	Reagent	Compound
I-1	 [34743-49-2]	 Co. No. 9
I-1	 [2091685-73-1]	 Co. No. 10
I-1	 [24596-18-7]	 Co. No. 11
I-1	 I-20	 Co. No. 12

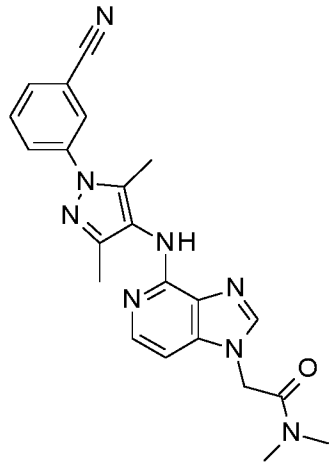
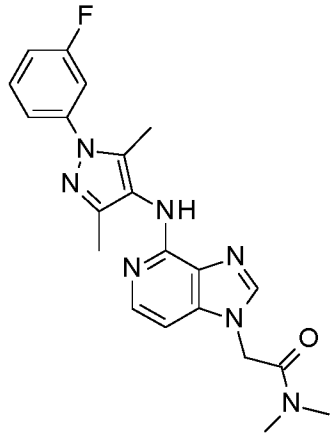
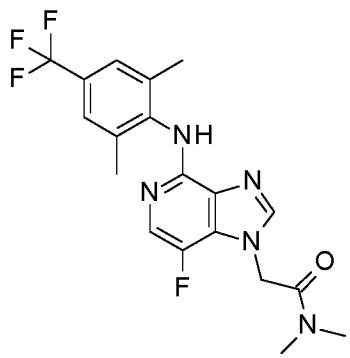
Starting material	Reagent	Compound
I-1	 I- 21	 Co. No. 13
I-1	I-15	 Co. No. 14
I-1	I-14	 Co. No. 15
I-1	 [1805647-51-1]	 Co. No. 16

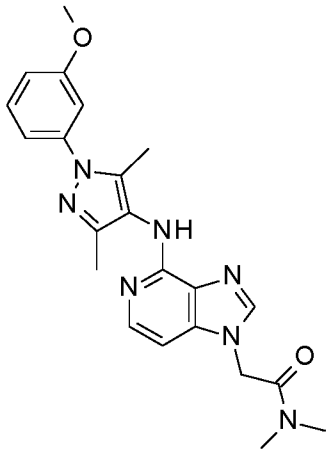
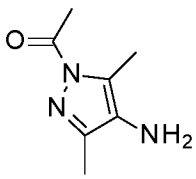
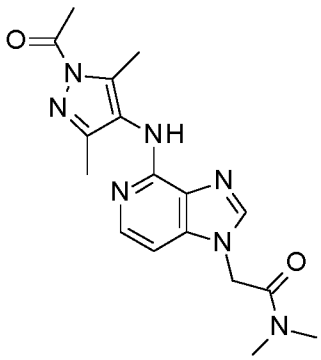
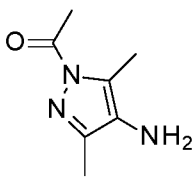
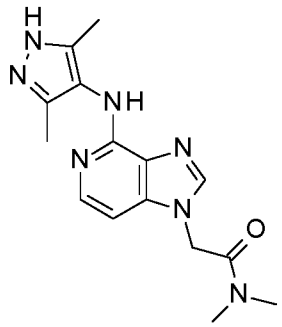
Starting material	Reagent	Compound
I-1	 [24279-39-8]	 Co. No. 17
I-1	 [6656-70-8]	 Co. No. 18
I-1	 [88-05-1]	 Co. No. 19
I-1	 [392-70-1]	 Co. No. 20

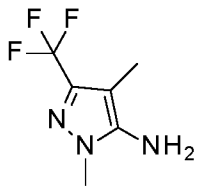
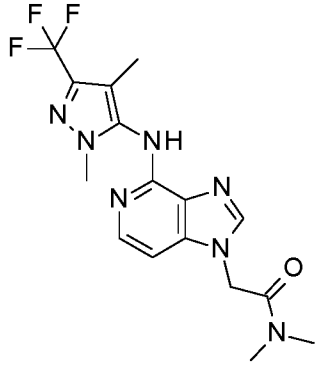
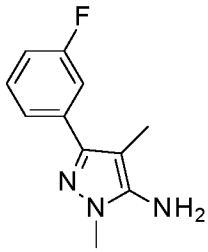
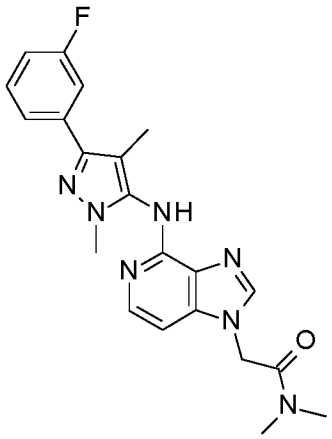
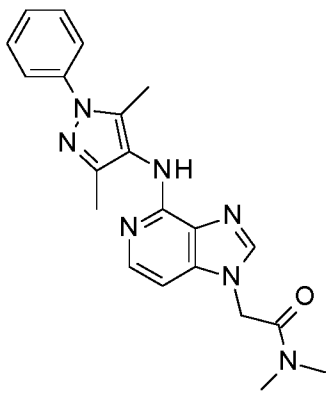
Starting material	Reagent	Compound
I-1	 [344-19-4]	 Co. No. 21
I-1	 I-26	 Co. No. 22
I-1	 I-27	 Co. No. 23
I-1	 [344-19-4]	 Co. No. 24

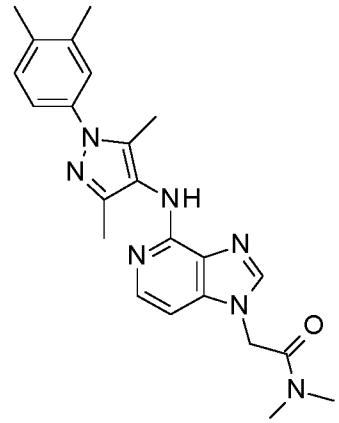
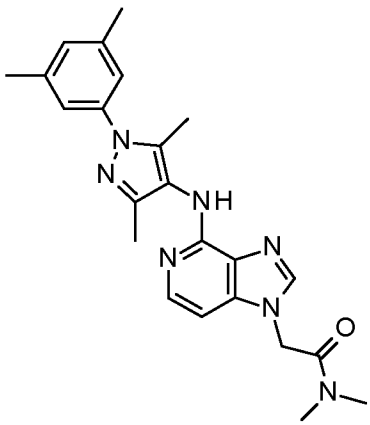
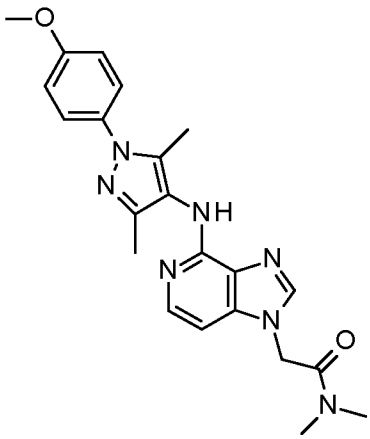
Starting material	Reagent	Compound
I-1	 [1806475-69-3]	 Co. No. 25
I-1	 [1464825-76-0]	 Co. No. 26
I-1	 Intermediate 28	 Co. No. 27
I-1	Intermediate 14	 Co. No. 28

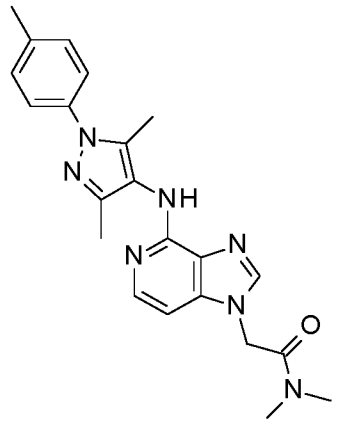
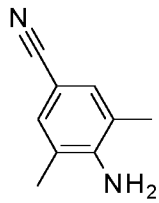
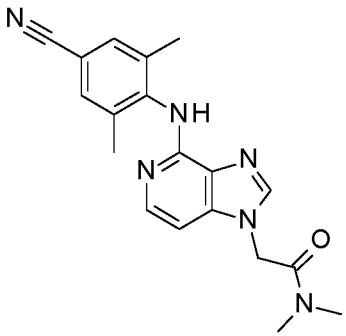
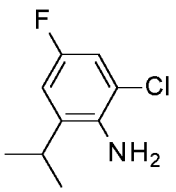
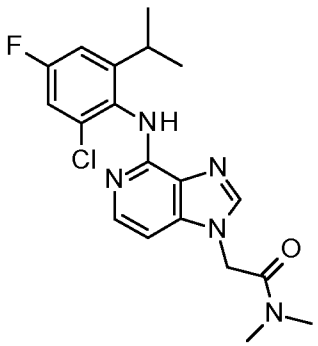
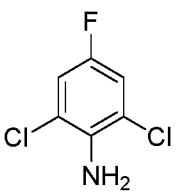
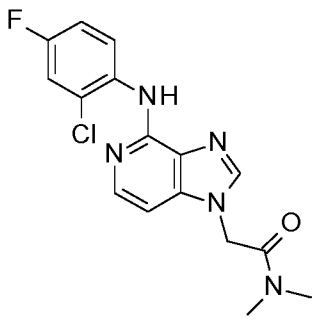
Starting material	Reagent	Compound
I-1	 [393-39-5]	 Co. No. 29
 I-29	I-17	 Co. No. 30
I-1	I-31	 Co. No. 31
I-1	I-32	 Co. No. 32

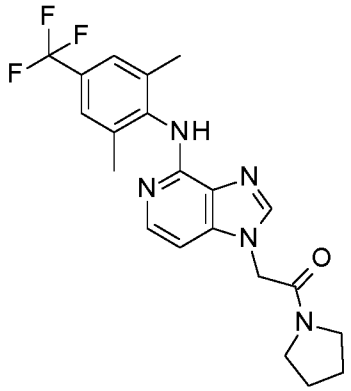
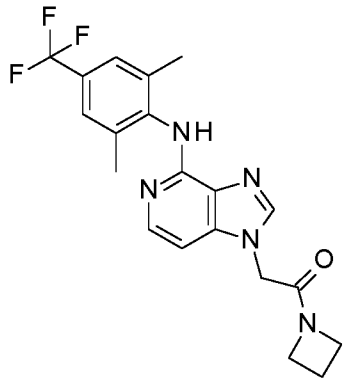
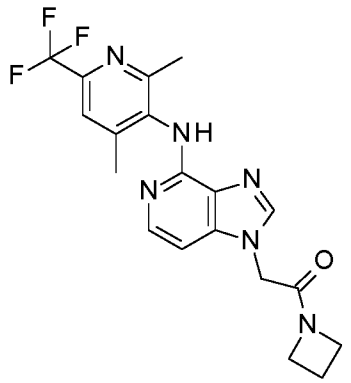
Starting material	Reagent	Compound
I-1	I-33	 Co. No. 33
I-1	I-34	 Co. No. 34
I-30	I-17	 Co. No. 35

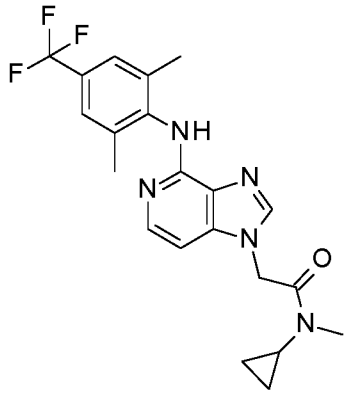
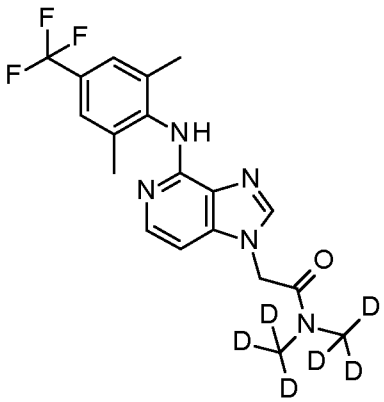
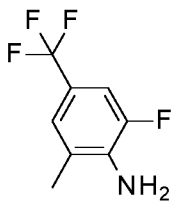
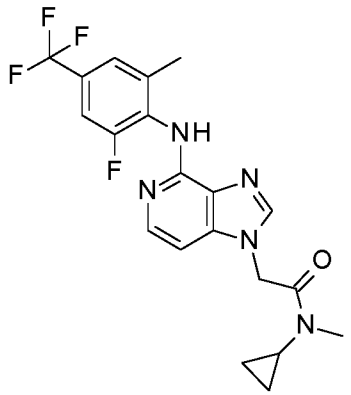
Starting material	Reagent	Compound
I-1	I-35	 Co. No. 36
I- 1	 [872407-86-8]	 Co. No. 37
I-1	 [872407-86-8]	 Co. No. 38

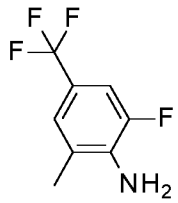
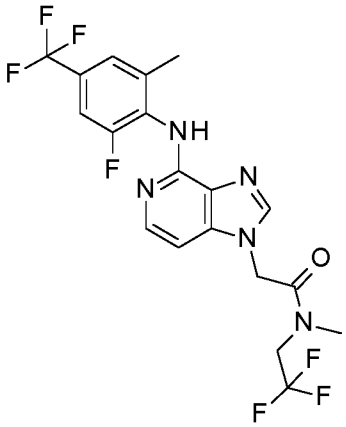
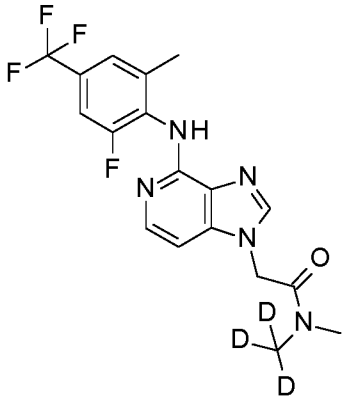
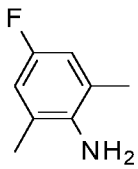
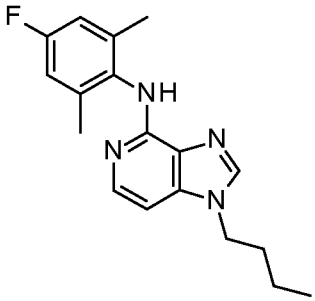
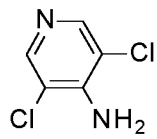
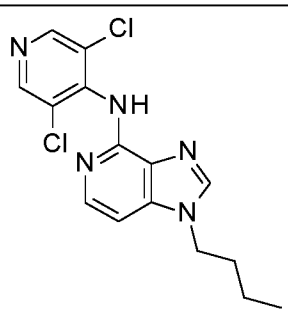
Starting material	Reagent	Compound
I-1	 [164668-13-7]	 Co. No. 39
I-1	 [1152663-40-5]	 Co. No. 40
I-1	I-36	 Co. No. 41

Starting material	Reagent	Compound
I-1	I-37	 Co. No. 42
I-1	I-38	 Co. No. 43
I-1	I-39	 Co. No. 44

Starting material	Reagent	Compound
I-1	I-40	 Co. No. 45
I-1	 [74896-24-5]	 Co. No. 46
I-1	 [1690442-59-1]	 Co. No. 47
I-1	 [344-19-4]	 Co. No. 48

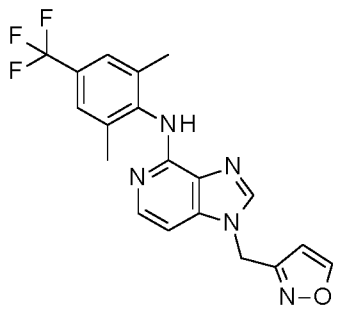
Starting material	Reagent	Compound
I-4	I-17	 Co. No. 49
I-3	I-17	 Co. No. 50
I-3	I-27	 Co. No. 51

Starting material	Reagent	Compound
I-6	I-17	 Co. No. 52
I-6	I-17	 Co. No. 53
I-6	 [1806475-69-3]	 Co. No. 54

Starting material	Reagent	Compound
I-9	 [1806475-69-3]	 Co. No. 55
I-12	I-17	 Co. No. 56
I-22	 [392-70-1]	 Co. No. 57
I-22	 [22889-78-7]	 Co. No. 58

COMPOUND 59

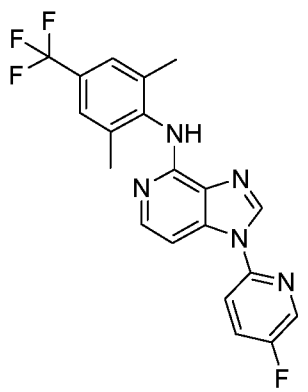
N-(2,6-dimethyl-4-(trifluoromethyl)phenyl)-1-(isoxazole-3-ylmethyl)-1H-imidazo[4,5-c]pyridine-4-amine



3-(Chloromethyl)isoxazole [57684-71-6] (32 µL, 0.34 mmol) was added to a stirred solution of I-46 (100 mg, 0.33 mmol) and K_2CO_3 [584-08-7] (55 mg, 0.39 mmol) in CH_3CN (1.5 mL). The reaction mixture was stirred at 75 °C for 16 h. The mixture was filtrated over Celite® and washed with a mixture of DCM/MeOH (9:1). The solvents were concentrated in vacuo and the residue was residue was purified by flash column chromatography on silica gel (dried load), using as eluent a gradient MeOH/DCM, 0/100 to 1.8/98.2. The desired fractions were collected and concentrated in vacuo. The residue was purified by reverse phase chromatography (Phenomenex Gemini C18 100x30mm 5µm Column; from 70% [25mM NH_4HCO_3] - 30% [ACN:MeOH (1:1)] to 27% [25mM NH_4HCO_3] - 73%[ACN:MeOH (1:1)]. The desired fractions were collected and concentrated in vacuo to yield Co.No. 59 as a white foamy solid (13 mg, 10%).

COMPOUND 60

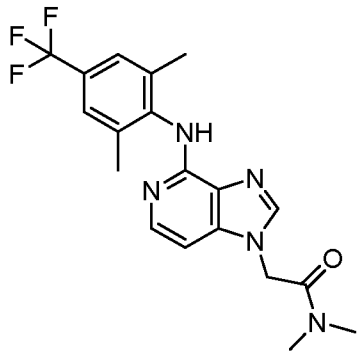
N-(2,6-Dimethyl-4-(trifluoromethyl)phenyl)-1-(5-fluoropyridin-2-yl)-1H-imidazo[4,5-c]pyridin-4-amine



A mixture of I-18 (142 mg, 0.57 mmol), I-17 (119 mg, 0.63 mmol) and Cs_2CO_3 (409 mg, 1.26 mmol), DMA (2.2 mL), was degassed with nitrogen. $Pd(OAc)_2$ [3375-31-3] (12.8 mg, 0.057 mmol) and Xantphos [161265-03-8] (33.1 mg, 0.057 mmol) were added and the mixture was heated at 120°C for 18h. The mixture was concentrated under reduced pressure. The residue was diluted with water, extracted with DCM, dried on $MgSO_4$, filtered and the solvents evaporated in vacuo. The crude product was purified by reverse phase chromatography (from 90% [0.1% HCOOH] - 10% [ACN: MeOH 1:1] to 54% [0.1% HCOOH] - 46% [ACN: MeOH 1:1]). The desired fractions were collected and concentrated in vacuo to yield Co. No. 60 as a white solid (80 mg, 35%).

COMPOUND 61

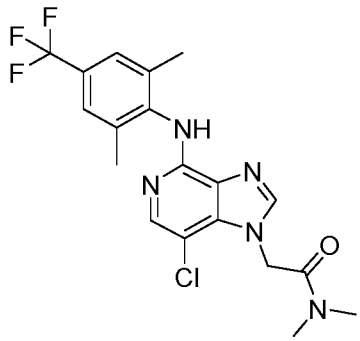
2-(4-((2,6-Dimethyl-4-(trifluoromethyl)phenyl)amino)-1H-imidazo[4,5-c]pyridin-1-yl)-N,N-dimethylacetamide



A mixture of I-1 (8.03 g, 33.64 mmol), I-17 (7.0 g, 37 mmol) and Cs_2CO_3 (24.1 g, 74 mmol) in DMA (104 mL) was degassed with nitrogen. Pd(OAc)2 [3375-31-3] (755 mg, 3.36 mmol) and Xantphos [161265-03-8] (1.95 g, 3.36 mmol) were added and the mixture was heated at 120 °C for 16h. After cooling, an aquoeus solution of 5% LiCl (100 ml) was added and the mixture was extracted with EtOAc (4x). The organic layer was separated and washed with more aqueous solution of 5% LiCl. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated in vacuo. The residue was purified by flash column chromatography (silica; 7M solution of ammonia in MeOH in DCM 0/100 to 4/96). The desired fractions were collected, and solvents evaporated in vacuo. The residue was triturated with Et2O. The solid was filtered off, washed with Et2O and dried at 50°C for 3 days in a desiccator to yield Co. No. 61 as an off white solid (7.9 g, 60%).

COMPOUND 62

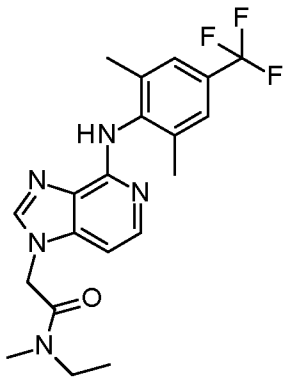
2-[7-Chloro-4-[2,6-dimethyl-4-(trifluoromethyl)anilino]imidazo[4,5-c]pyridin-1-yl]-N,N-dimethyl-acetamide



NCS [128-09-6] (38 mg, 0.28 mmol) was added portionwise to a solution of compound 61 (100 mg, 0.26 mmol) in DMF (1 mL). The reaction mixture was stirred at room temperature 16 h. The mixture was diluted with sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated in vacuo. The crude was purified by reverse phase (Phenomenex Gemini C18 100x30mm 5µm Column; from 81% [0.1% HCOOH] - 19% [ACN:MeOH (1:1)] to 45% [0.1% HCOOH] - 55% [ACN:MeOH (1:1)]). The desired fractions were collected and concentrated. The product was tritured with DIPE to yield Co. No. 62 as an off white solid (52 mg, 47%).

COMPOUND 63

2-[4-[2,6-Dimethyl-4-(trifluoromethyl)anilino]imidazo[4,5-c]pyridin-1-yl]-N-ethyl-N-methyl-acetamide

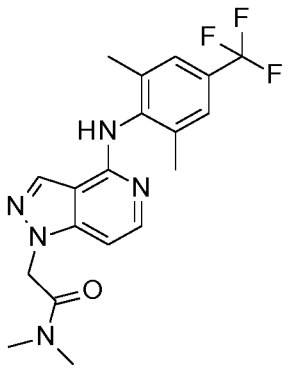


N-Methylimidazole [616-47-7] (36 µL, 0.742 g/mL, 0.327 mmol) was added to a

stirred solution of I-18 (70 mg, 0.19 mmol) and N-ethylmethylamine [624-78-2] (25 µL, 0.688 g/mL, 0.288 mmol) in NMP [872-50-4] (1.18 mL) and ACN (0.589 mL) at RT. The reaction was heated at 65 °C for 15 min until homogeneus solution. HOBt [123333-53-9] (39 mg, 0.29 mmol) and EDC-HCl [25952-53-8] (53 mg, 0.27 mmol) were added at RT and the RM was stirred at 65 °C for 1.5 h. The RM was quenched with sat. $NaHCO_3$ at 0 °C and extracted with EtOAc. The organic layer was separated, dried over MgSO4, filtered and the solvents evaporated in vacuo. The resulting residue was purified by flash column chromatography on silica gel, using as eluent a gradient MeOH in DCM 0/100 to 10/90 to yield 69 mg (87%) of Co. No. 63 as a white solid, after trituration with DIPE.

COMPOUND 64

2-[4-[2,6-Dimethyl-4-(trifluoromethyl)anilino]pyrazolo[4,3-c]pyridin-1-yl]-N,N-dimethyl-acetamide

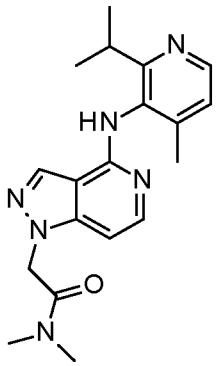


Pd_2dba_3 [51364-51-3] (9.7 mg, 0.017 mmol) was added to a degassed solution of cesium carbonate [534-17-8] (330 mg, 1.01 mmol) and XantPhos [161265-03-8] (19.5 mg, 0.034 mmol) in DMF (15 mL) under a N_2 flow. The resulting mixture was stirred for 2 min at 40 °C, then I-43 (100 mg, 0.34 mmol) was added under a N_2 flow. The mixture was stirred at 40 °C for another 5 min, then finally [2-iodo-1,3-dimethyl-5-(trifluoromethyl)benzene [875550-67-7] (121.5 mg, 0.41 mmol) was added and the RM was stirred for 18 h at 85 °C. Water was added and the mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo to provide a residue which was combined with a crude from an analogous procedure performed on 100 mg (0.34 mmol) of I-43 and the resulting mixture was purified via flash column chromatography using as eluent a gradient DCM/MeOH (20:1) in DCM, 0/100 to 5/95). The desired fractions were collected and concentrated

in vacuo. The resulting residue was triturated with diethyl ether and filtered to yield Co. No. 64 (261 mg, 99% yield) as a white pale solid.

COMPOUND 65

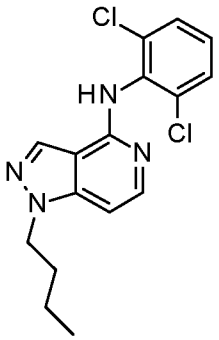
2-[4-[(2-Isopropyl-4-methyl-3-pyridyl)amino]pyrazolo[4,3-c]pyridin-1-yl]-N,N-dimethyl-acetamide



Pd_2dba_3 [51364-51-3] (4.5 mg, 0.0078 mmol) was added to a solution of Cs_2CO_3 [534-17-8] (151.5 mg, 0.46 mmol) and XantPhos [161265-03-8] (9.0 mg, 0.015 mmol) in DMF (15 mL) under a N_2 flow and the mixture was stirred for 2 min at 40 °C. I-41 (50 mg, 0.155 mmol, a batch of 74% purity) was added under N_2 flow and the resulting mixture was stirred at 40 °C for 5 min, then 4-methyl-2-(1-methylethyl)-3-pyridinamine [1698293-93-4] (28 mg, 0.18 mmol) was added. The RM was stirred for 18 h at 85 °C. The RM was evaporated under reduced pressure, then the resulting residue was combined with a crude from an analogous procedure performed on 100 mg (0.31 mmol, 74% purity) of I-41 and it was purified by Prep HPLC (Stationary phase: XBridge Prep C18 3.5µm, 4.6x100mm; mobile phase: from 95% [65mM NH_4OAc + ACN (90:10)] - 5% [100% de Acetonitrile] to 63% [65mM NH_4OAc + ACN (90:10)] - 37% [100% de Acetonitrile]) to afford Co. No. 65 (38 mg, 23%).

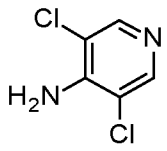
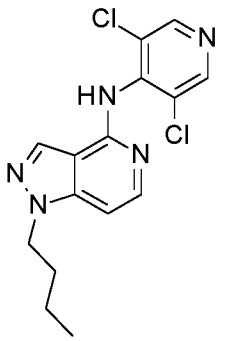
COMPOUND 66

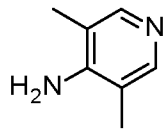
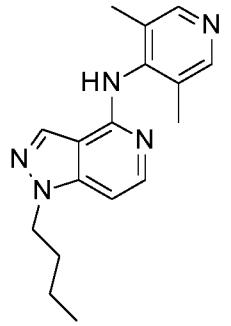
1-Butyl-N-(2,6-dichlorophenyl)pyrazolo[4,3-c]pyridin-4-amine



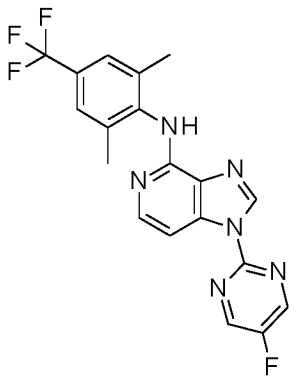
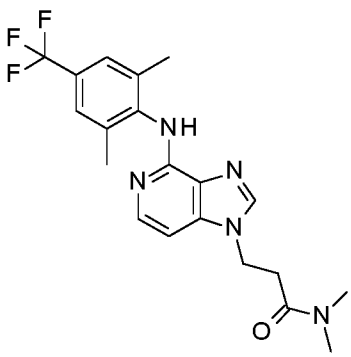
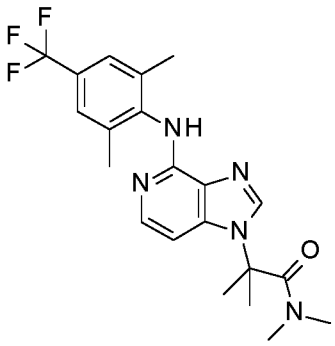
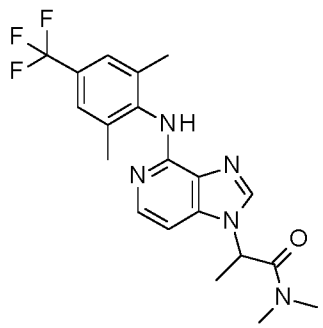
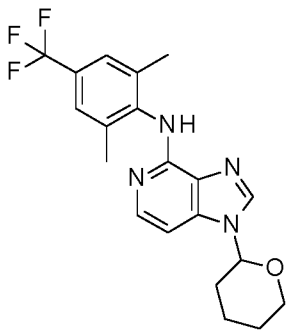
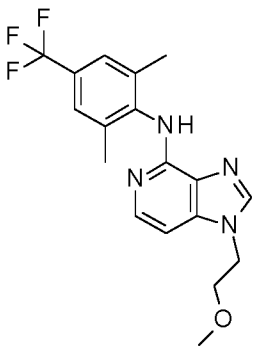
A mixture of I-44 (120 mg, 0.57 mmol), 2,6-dichloroaniline [608-31-1] (464 mg, 2.86 mmol) and Cs_2CO_3 [534-17-8] (0.522 g, 1.60 mmol) in tBuOH (2.3 mL) was degassed with N_2. $Pd(OAc)_2$ [3375-31-3] (5 mg, 0.023 mmol) and Xantphos [161265-03-8] (13 mg, 0.023 mmol) were added and the mixture was heated at 80 °C during 1 h. The solvent was removed in vacuo and the resulting residue was diluted with water and extracted with DCM. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced presure. The resulting residue was purified by RP (Solid Phase: XBridge C18_3.5 µm, 100 x 4.6 mm, Mobile phase: 0.2% NH_4HCO_3 + MeOH) to afford Co. No. 66 (90 mg, 47%) as a white solid.

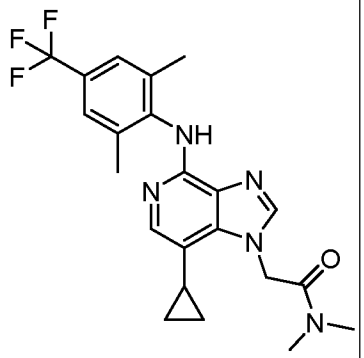
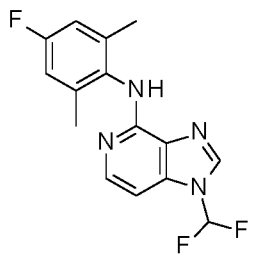
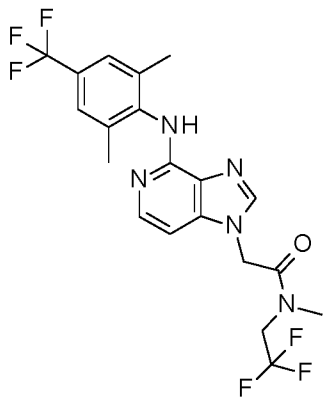
The following compounds were synthesized in an analogous manner from the indicated intermediates and reagents:

Starting material	Reagent	Compound
	 [22889-78-7]	 Co. No. 67

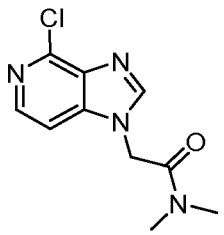
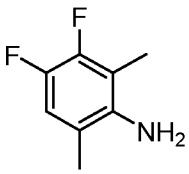
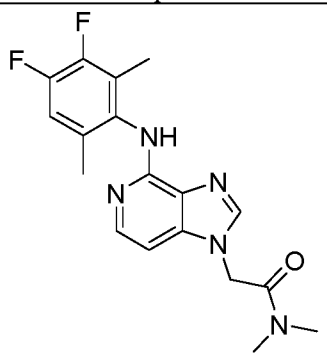
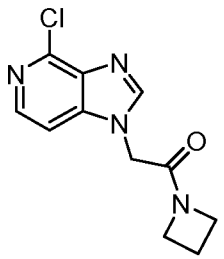
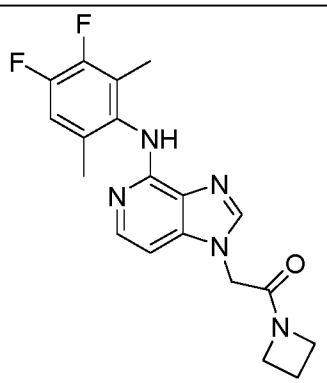
Starting material	Reagent	Compound
I-44	 [265981-13-3]	 Co. No. 68

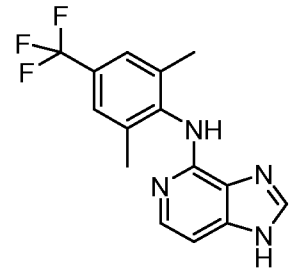
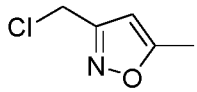
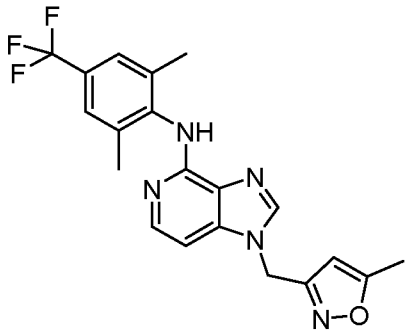
The following compounds were also made according to procedures analogous to those described herein:

 Co. No. 69	 Co. No. 70	 Co. No. 71
 Co. No. 72	 Co. No. 73	 Co.No. 74

 Co.No. 75	 Co.No. 76	 Co.No. 77

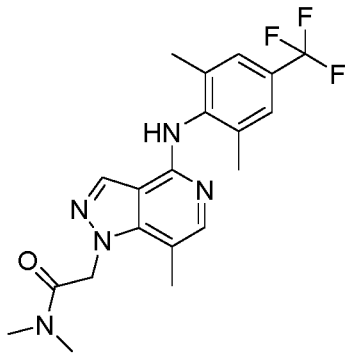
The following compounds were made according to procedures analogous to those described herein from the indicated intermediates and reagents:

Starting material	Reagent	Compound
 I-1	 I-45	 Co. No. 78
 I-3	I-45	 Co. No. 79

Starting material	Reagent	Compound
 I-46	 [35166-37-1]	 Co. No. 80

COMPOUND 81

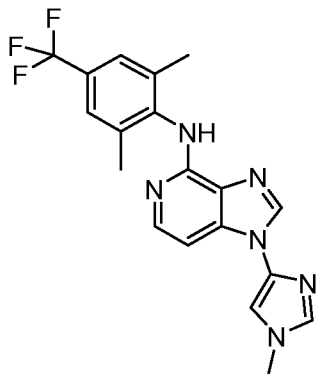
2-(4-((2,6-Dimethyl-4-(trifluoromethyl)phenyl)amino)-7-methyl-1H-pyrazolo[4,3-c]pyridin-1-yl)-N,N-dimethylacetamide



Compound 81 was prepared similarly as described for the synthesis of compound 6 starting from compound 64.

COMPOUND 82

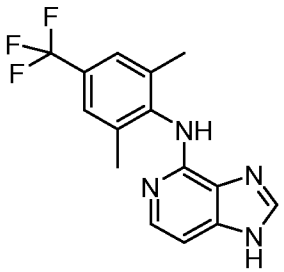
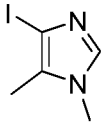
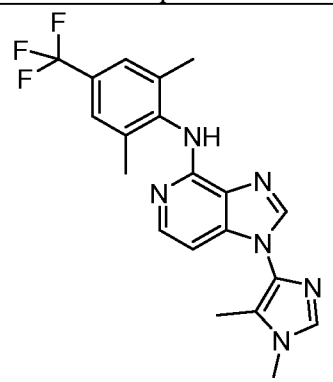
N-(2,6-dimethyl-4-(trifluoromethyl)phenyl)-1-(1-methyl-1H-imidazol-4-yl)-1H-imidazo[4,5-c]pyridin-4-amine



I-46 (120 mg, 0.39 mmol), 4-iodo-1-methyl-1H-imidazole [71759-87-0] (166 mg, 0.78 mmol) and potassium phosphate [7778-53-2] (336 mg, 1.57 mmol) were diluted in

diglyme anhydrous [111-96-6] (3 mL, previously degassed with nitrogen for 5 min.) in a sealed tube under nitrogen. Then, copper (I) iodide [7681-65-4] (23 mg, 0.12 mmol) and trans-1,2-cyclohexanediamine [1121-22-8] (14 µL, 0.12 mmol) were added and the mixture was stirred at 120 °C for 16 h. The mixture was filtrated over Celite® and washed with a mixture of DCM/MeOH (9:1). The solvents were concentrated in vacuo and the residue was residue was purified by flash column chromatography on silica gel (dried load), using as eluent a gradient MeOH/DCM, 0/100 to 2/98. The desired fractions were collected and concentrated in vacuo to yield Co. No. 82 (36 mg, 22%) as a yellow sticky solid.

The following compounds were synthesized in an analogous manner from the indicated Intermediates and reagents

Starting material	Reagent	Compound
 I-46	 I-14 [133838-77-4]	 Co. No. 83

ANALYTICAL PART

MELTING POINTS

Values are either peak values or melt ranges and are obtained with experimental uncertainties that are commonly associated with this analytical method.

DSC823e or DSC1 STAR (indicated as (a)) & Mettler Toledo MP50:

For several compounds, melting points were determined with a DSC823e or a DSC1 STAR (Mettler-Toledo). Melting points were measured with a temperature gradient of 10°C/minute. Maximum temperature was 300°C.

For several compounds, melting points were determined with a MP50 (Mettler-Toledo) (indicated as (b)). Melting points were measured with a temperature gradient of 10°C/minute.

LCMS

GENERAL PROCEDURE

The High-Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time…) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW) and/or exact mass monoisotopic molecular weight. Data acquisition was performed with appropriate software.

Compounds are described by their experimental retention times (R_t) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the $[M+H]^+$ (protonated molecule) and/or $[M-H]^-$ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. $[M+NH_4]^+$, $[M+HCOO]^-$, $[M+CH_3COO]^-$ etc…). For molecules with multiple isotopic patterns (Br, Cl..), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "SQD" Single Quadrupole Detector, "MSD" Mass Selective Detector, "QTOF" Quadrupole-Time of Flight, "rt" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, HSS" High Strength Silica, "CSH" charged surface hybrid, "UPLC" Ultra Performance Liquid Chromatography, "DAD" Diode Array Detector.

TABLE 1. LC-MS Methods (Flow expressed in mL/min; column temperature (T) in °C; Run time in min).

Method code	Instrument	Column	Mobile phase	Gradient	Flow ------- Col T	Run time (min)
1	Waters: Acquity® UPLC® - DAD and SQD	Waters : HSS T3 (1.8µm, 2.1*100mm)	A: 10mM CH_3COONH_4 in 95% H_2O +	From 100% A to 5% A in 2.10min,	0.6 ------- 55	3.5

Method code	Instrument	Column	Mobile phase	Gradient	Flow ------- Col T	Run time (min)
			5% CH_3CN B: CH_3CN	to 0% A in 0.90min, to 5% A in 0.5min		
2	Waters: Acquity® UPLC® -DAD and SQD	Waters : BEH (1.8µm, 2.1*100mm)	A: 10mM CH_3COONH_4 in 95% H_2O + 5% CH_3CN B: CH_3CN	From 100% A to 5% A in 2.10min, to 0% A in 0.90min, to 5% A in 0.5min	0.6 ------- 55	3.5
3	Agilent: 1100-DAD and MSD	YMC: Pack ODS-AQ (3µm, 4.6x50mm)	A: HCOOH 0.1% in water, B: CH_3CN	95% A to 5% A in 4.8min, held for 1 min, back to 95% A in 0.2min.	2.6	6

TABLE 2. Analytical data –LCMS: $[M+H]^+$ means the protonated mass of the free base of the compound, $[M-H]^-$ means the deprotonated mass of the free base of the compound or the type of adduct specified $[M+CH_3COO]^-$). R_t means retention time (in min). For some compounds, exact mass was determined.

Co. No.	Mp (°C)	Rt	UV Area %	$[M+H]^+$	$[M-H]^-$
1		0.75	97.57	346	344
2		2.06	100	405	403
3	174.99	0.86	98.14	339	397 $[M+CH_3COO^-]$
4	275.1	1.85	99	378	
5	266.8	1.82	99	364	
6	238.3	2.05	99	406	
7	201.5	2.05	99	448	
8	230.0	1.56	96	354.1	
9	186.5	1.99	99	408	
10	211.6	2.197	99	406.17	
11	209.8	1.77	99	358	
12	234.4	2.27	99	420	
13	265.1	1.42	99	378	
14	223.3	0.56	100	353	-

Co. No.	Mp (°C)	Rt	UV Area %	$[M+H]^+$	$[M-H]^-$
15	214.14	1.76	100	412	410
16	182.81	0.92	98.5	428	426
17	238.4	2.04	99	432	
18	250	1.87	99	392	
19	270.2	1.68	99	338	
20	216.7	1.15	99	342	
21	243.4	1.48	99	382	
22	234.4	1.98	99	432	
23	233.3	1.515	99	393.1	
24	219.9	1.60	99	416	
25	226.6	1.84	99	396	
26		1.47	95.98	346	404$[M+CH_3COO^-]$
27	216.6	1.12	99	361.16	
28	236.6	1.97	99	406.1	
29	246.7	1.55	99	382	
30	188.2	2.13	99	406	
31	191.4	2.25	96	424	
32	256.6	1.58	99	409	
33	239.9	1.62	99	415.2	
34	181.5	1.71	95	408.1	
35	236.7	2.39	99	410.1	
36	179.7	1.74	95	420	
37	175.4	1.25	97	356	
38	283.5	0.85	98	314	
39	240.0	1.63	99	382.1	
40	230	1.89	99	408.2	
41	126.3	1.71	99	390.2	
42	144.7	2.05	96	418.2	
43	154.7	2.09	97	418.2	
44	199.9	1.83	99	420.0	
45	214.9	1.95	99	404.2	
46	263.4	1.425	99	349.1	
47	251.8	1.85	98	390	
48	>300	1.99	99	346	
49	196.6	2.09	99	418	
50	176.4	1.93	99	404	
51		1.53	98	405	
52	199.8	2.19	99	418.2	

Co. No.	Mp (°C)	Rt	UV Area %	$[M+H]^+$	$[M-H]^-$
53	208.2	1.99	99	398.2	
54	219.8	2.18	99	422	
55	238.3	2.39	99	464	
56	212.2	1.94	99	395.1	
57	184.45	1.97	96.81	313	
58		1.74	100	336	334
59	154.7	2.222	99	388.1	
60	186.5	2.38	99	402	
61	207.65	1.92	100	392.2	390.2
62	239.9	2.78	98	426	
63	186.5 (b)	1.97	99	406	
64	196.5(b)	2.09	99	392	
65	211.5(b)	1.3	98	353	
66	144.7(a)	1.97	96.09	335	333
67		1.8	99.16	336	334
68		1.65	97.5	296	294
69	198.2 (b)	2.57	98	403	
70	194.9 (b)	2.12	97	406	
71	260.1 (b)	2.21	99	420	
72	199.9 (b)	2.13	99	406	
73	169.8 (b)	2.44	97	391.1	
74	161.5 (b)	2.20	98	365.1	
75	246.7 (b)	2.30	99	432.2	
76	194.8 (b)	1.77	99	307.1	
77	228.3 (b)	2.42	99	460.1	
78	198.1 (b)	1.63	96	360	
79	214.8 (b)	1.65	99	372	
80	164.7 (b)	2.30	99	402.1	
81	211.6 (b)	2.20	99	406.1	
82	184.8 (b)	2.15	99	387.1	
83		2.20	95	401.1	

NMR

For a number of compounds, ^{1}H NMR spectra were recorded on a Bruker AV III HD spectrometer operating at 400 MHz, on a Bruker Avance NEO operating at 500 MHz, or on a Bruker Avance NEO spectrometer operating at 400 MHz, using

CHLOROFORM-*d* (deuterated chloroform, $CDCl_3$) or DMSO-d_6 (deuterated DMSO, dimethyl-d6 sulfoxide) as solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as internal standard.

Co. No. 10: ^{1}H NMR (400 MHz, DMSO) δ = 8.42 (s, 1H), 8.03 (s, 1H), 7.58 (d, *J*=5.8, 1H), 7.46 (s, 1H), 7.43 (s, 1H), 6.81 (d, *J*=5.8, 1H), 5.22 (s, 2H), 3.11 (s, 3H), 2.88 (s, 3H), 2.62 (q, *J*=7.5, 2H), 2.19 (s, 3H), 1.06 (t, *J*=7.5, 3H).

Co. No. 12: ^{1}H NMR (400 MHz, DMSO) δ = 8.41 (s, 1H), 8.03 (s, 1H), 7.57 (d, *J*=5.8, 1H), 7.49 – 7.40 (m, 2H), 6.79 (d, *J*=5.8, 1H), 5.22 (s, 2H), 3.29 – 3.17 (m, 1H), 3.11 (s, 3H), 2.88 (s, 3H), 2.18 (s, 3H), 1.10 (d, *J*=6.9, 6H).

Co. No. 13: ^{1}H NMR (400 MHz, DMSO) δ = 8.15 (s, 1H), 8.02 – 7.98 (m, 2H), 7.52 (d, *J*=5.7, 1H), 7.30 (s, 1H), 6.74 (d, *J*=5.8, 1H), 5.21 (s, 2H), 4.00 (s, 3H), 3.11 (s, 3H), 2.88 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H).

Co. No. 42: ^{1}H NMR (400 MHz, DMSO) δ 8.43 (br s, 1H), 8.04 (s, 1H), 7.59 (d, *J* = 5.8 Hz, 1H), 7.45 (s, 2H), 6.82 (d, *J* = 5.8 Hz, 1H), 5.22 (s, 2H), 2.21 (s, 6H).

Co. No. 45: ^{1}H NMR (400 MHz, DMSO) δ = 8.05 (s, 1H), 8.01 (s, 1H), 7.65 (d, *J*=5.8, 1H), 7.41 (d, *J*=8.4, 2H), 7.31 (d, *J*=8.2, 2H), 6.79 (d, *J*=5.8, 1H), 5.22 (s, 2H), 3.11 (s, 3H), 2.88 (s, 3H), 2.37 (s, 3H), 2.16 (s, 3H), 2.05 (s, 3H).

Co. No. 47: ^{1}H NMR (400 MHz, DMSO) δ 8.35 (s, 1H), 8.02 (s, 1H), 7.58 (d, *J* = 5.8 Hz, 1H), 7.30 (dd, *J* = 8.3, 2.9 Hz, 1H), 7.18 (dd, *J* = 10.0, 2.9 Hz, 1H), 6.79 (d, *J* = 5.8 Hz, 1H), 5.22 (s, 2H), 3.25 – 3.15 (m, 1H), 3.11 (s, 3H), 2.88 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 6H).

Co. No. 52: ^{1}H NMR (400 MHz, DMSO) δ = 8.43 (s, 1H), 8.08 (s, 1H), 7.59 (d, *J*=5.8, 1H), 7.45 (s, 2H), 6.85 (d, *J*=5.8, 1H), 5.32 (s, 2H), 3.00 – 2.92 (m, 1H), 2.85 (s, 3H), 2.22 (s, 6H), 1.00 – 0.88 (m, 4H).

Co. No. 53: ^{1}H NMR (400 MHz, DMSO) δ 8.43 (br s, 1H), 8.04 (s, 1H), 7.59 (d, *J* = 5.8 Hz, 1H), 7.45 (s, 2H), 6.82 (d, *J* = 5.8 Hz, 1H), 5.22 (s, 2H), 2.21 (s, 6H)

Co. No. 59: ^{1}H NMR (400 MHz, DMSO) δ 8.92 (d, *J* = 1.6 Hz, 1H), 8.51 (br s, 1H), 8.31 (s, 1H), 7.62 (d, *J* = 5.8 Hz, 1H), 7.44 (s, 2H), 6.85 (d, *J* = 5.8 Hz, 1H), 6.62 (d, *J* = 1.6 Hz, 1H), 5.62 (s, 2H), 2.19 (s, 6H).

Co. No. 61: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 6 H), 2.88 (s, 3 H), 3.12 (s, 3 H), 5.23 (s, 2 H), 6.82 (d, *J* = 5.70 Hz, 1 H), 7.45 (s, 2 H), 7.59 (d, *J* = 5.70 Hz, 1 H), 8.04 (s, 1 H), 8.42 (s, 1 H).

Co. No. 63: ^{1}H NMR (400 MHz, DMSO) δ 8.43 (s, 3H), 8.06 (d, *J* = 12.2 Hz, 3H), 7.59 (d, *J* = 5.8 Hz, 3H), 7.45 (s, 6H), 6.80 (dd, *J* = 12.1, 5.8 Hz, 3H), 5.24 (s, 0.9H), 5.20 (s, 1.1H), 3.09 (s, 1.7H), 2.85 (s, 1.3H), 2.21 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 1.3H), 1.04 (t, *J* = 7.1 Hz, 1.7H). Two rotamers were observed, ratio 60:40.

Co. No. 64: ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.31 (s, 6 H), 3.00 (s, 3 H), 3.14 (s, 3 H), 5.12 (s, 2 H), 6.55 (br s, 1 H), 6.75 (br d, *J* = 6.05 Hz, 1 H), 6.94 (s, 1 H), 7.46 (s, 2 H), 7.95 (br d, *J* = 5.91 Hz, 1 H).

Co. No. 65: ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.15 - 1.23 (m, 6 H) 2.23 (s, 3 H) 2.99 (s, 3 H) 3.11 (s, 3 H) 3.37 - 3.58 (m, 1 H) 5.11 (s, 2 H) 6.73 (br d, *J*=5.91 Hz, 1 H) 6.82 (br s, 1 H) 7.13 (br d, *J*=4.67 Hz, 1 H) 7.91 (br d, *J*=5.91 Hz, 1 H) 8.53 (d, *J*=4.67 Hz, 1 H)

Co. No. 66: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.88 (t, *J* = 7.37 Hz, 3 H), 1.24 (sxt, *J* = 7.44 Hz, 2 H), 1.78 (quin, *J* = 7.21 Hz, 2 H), 4.29 (t, *J* = 6.93 Hz, 2 H), 6.87 (br d, *J* = 5.50 Hz, 1 H), 7.26 - 7.35 (m, 1 H), 7.55 (d, *J* = 8.14 Hz, 2 H), 7.59 (br s, 1 H), 7.99 (br s, 1 H), 9.38 (br s, 1 H).

Co. No. 67: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.94 (t, *J* = 7.32 Hz, 3 H), 1.26 - 1.38 (m, 2 H), 1.77 - 1.96 (m, 2 H), 4.21 - 4.29 (m, 2 H), 6.57 (d, *J* = 6.92 Hz, 1 H), 7.41 (s, 1 H), 7.48 (d, *J* = 6.51 Hz, 1 H), 8.49 (s, 2 H), 9.43 (br s, 1 H).

Co. No. 68: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.94 (t, *J* = 7.37 Hz, 3 H), 1.22 - 1.38 (m, 2 H), 1.78 - 1.94 (m, 2 H), 1.94 - 2.17 (m, 1 H), 2.20 (s, 6 H), 4.26 (t, *J* = 7.15 Hz, 2 H), 6.72 (d, *J* = 6.16 Hz, 1 H), 7.18 (s, 1 H), 7.84 (br d, *J* = 6.16 Hz, 1 H), 8.39 (s, 2 H).

Co. No. 78: 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.20 (d, J=2.4 Hz, 3 H) 2.21 (s, 3 H) 3.05 (s, 3 H) 3.17 (s, 3 H) 4.93 (s, 2 H) 6.65 (d, J=5.9 Hz, 1 H) 6.75 (br s, 1 H) 6.89 - 6.97 (m, 1 H) 7.83 (s, 1 H) 7.88 (d, J=5.8 Hz, 1 H).

PHARMACOLOGICAL EXAMPLES

1) OGA – BIOCHEMICAL ASSAY

The assay is based on the inhibition of the hydrolysis of fluorescein mono-ß-D-N-Acetyl-Glucosamine (FM-GlcNAc) (Mariappa et al. 2015, Biochem J 470:255) by the recombinant human Meningioma Expressed Antigen 5 (MGEA5), also referred to as O-GlcNAcase (OGA). The hydrolysis FM-GlcNAc (Marker Gene technologies, cat #

M1485) results in the formation of ß-D-N-glucosamineacetate and fluorescein. The fluorescence of the latter can be measured at excitation wavelength 485 nm and emission wavelength 538nm. An increase in enzyme activity results in an increase in fluorescence signal. Full length OGA enzyme was purchased at OriGene (cat # TP322411). The enzyme was stored in 25 mM Tris.HCl, pH 7.3, 100 mM glycine, 10% glycerol at -20 °C. Thiamet G and GlcNAcStatin were tested as reference compounds (Yuzwa et al. 2008 Nature Chemical Biology 4:483; Yuzwa et al. 2012 Nature Chemical Biology 8:393). The assay was performed in 200mM Citrate/phosphate buffer supplemented with 0.005% Tween-20. 35.6 g Na_2HPO_4 2 H_2O (Sigma, # C0759) were dissolved in 1 L water to obtain a 200 mM solution. 19.2 g citric acid (Merck, # 1.06580) was dissolved in 1 L water to obtain a 100 mM solution. pH of the sodiumphosphate solution was adjusted with the citric acid solution to 7.2. The buffer to stop the reaction consists of a 500 mM Carbonate buffer, pH 11.0. 734 mg FM-GlcNAc were dissolved in 5.48 mL DMSO to obtain a 250 mM solution and was stored at -20 °C. OGA was used at a 2nM concentration and FM-GlcNAc at a 100uM final concentration. Dilutions were prepared in assay buffer.

50 nl of a compound dissolved in DMSO was dispensed on Black Proxiplate TM 384 Plus Assay plates (Perkin Elmer, #6008269) and 3 µl fl-OGA enzyme mix added subsequently. Plates were pre-incubated for 60 min at room temperature and then 2 µl FM-GlcNAc substrate mix added. Final DMSO concentrations did not exceed 1%. Plates were briefly centrifuged for 1 min at 1000rpm and incubate at room temperature for 6 h. To stop the reaction 5 µl STOP buffer were added and plates centrifuge again 1 min at 1000rpm. Fluorescence was quantified in the Thermo Scientific Fluoroskan Ascent or the PerkinElmer EnVision with excitation wavelength 485 nm and emission wavelength 538 nm.

For analysis a best-fit curve is fitted by a minimum sum of squares method. From this an IC_{50} value and Hill coefficient was obtained. High control (no inhibitor) and low control (saturating concentrations of standard inhibitor) were used to define the minimum and maximum values.

2) OGA - CELLULAR ASSAY

HEK293 cells inducible for P301L mutant human Tau (isoform 2N4R) were established at Janssen. Thiamet-G was used for both plate validation (high control) and as reference compound (reference EC_{50} assay validation). OGA inhibition is evaluated through the immunocytochemical (ICC) detection of O-GlcNAcylated proteins by the use of a

monoclonal antibody (CTD110.6; Cell Signaling, #9875) detecting O-GlcNAcylated residues as previoulsy described (Dorfmueller et al. 2010 Chemistry & biology, 17:1250). Inhibition of OGA will result in an increase of O- GlcNAcylated protein levels resulting in an increased signal in the experiment. Cell nuclei are stained with Hoechst to give a cell culture quality control and a rough estimate of immediate compounds toxicity, if any. ICC pictures are imaged with a Perkin Elmer Opera Phenix plate microscope and quantified with the provided software Perkin Elmer Harmony 4.1.

Cells were propagated in DMEM high Glucose (Sigma, #D5796) following standard procedures. 2 days before the cell assay cells are split, counted and seeded in Poly-D-Lysine (PDL) coated 96-wells (Greiner, #655946) plate at a cell density of 12,000 cells per cm^2 (4,000 cells per well) in 100µl of Assay Medium (Low Glucose medium is used to reduce basal levels of GlcNAcylation) (Park et al. 2014 The Journal of biological chemistry 289:13519). At the day of compound test medium from assay plates was removed and replenished with 90µl of fresh Assay Medium. 10µl of compounds at a 10fold final concentration were added to the wells. Plates were centrifuged shortly before incubation in the cell incubator for 6 hours. DMSO concentration was set to 0.2%. Medium is discarded by applying vacuum. For staining of cells medium was removed and cells washed once with 100 µl D-PBS (Sigma, #D8537). From next step onwards unless other stated assay volume was always 50µl and incubation was performed without agitation and at room temperature. Cells were fixed in 50µl of a 4% paraformaldehyde (PFA, Alpha aesar, # 043368) PBS solution for 15 minutes at room temperature. The PFA PBS solution was then discarded and cells washed once in 10mM Tris Buffer (LifeTechnologies, # 15567-027), 150mM NaCl (LifeTechnologies, #24740-0110, 0.1% Triton X (Alpha aesar, # A16046), pH 7.5 (ICC buffer) before being permeabilized in same buffer for 10 minutes. Samples are subsequently blocked in ICC containing 5% goat serum (Sigma, #G9023) for 45-60 minutes at room temperature. Samples were then incubated with primary antibody (1/1000 from commercial provider, see above) at 4°C overnight and subsequently washed 3 times for 5 minutes in ICC buffer. Samples were incubated with secondary fluorescent antibody (1/500 dilution, Lifetechnologies, # A-21042) and nuclei stained with Hoechst 33342 at a final concentration of 1µg/ml in ICC (Lifetechnologies, # H3570) for 1 hour. Before analysis samples were washed 2 times manually for 5 minutes in ICC base buffer.

Imaging is performed using Perkin Elmer Phenix Opera using a water 20x objective and recording 9 fields per well. Intensity readout at 488nm is used as a measure of O-GlcNAcylation level of total proteins in wells. To assess potential toxicity of compounds nuclei were counted using the Hoechst staining. IC_{50}-values are calculated

using parametric non-linear regression model fitting. As a maximum inhibition Thiamet G at a 200uM concentration is present on each plate. In addition, a concentration response of Thiamet G is calculated on each plate.

TABLE 5. Results in the biochemical and cellular assays. Representative compounds of the present invention were tested according to the procedure as described above, with results as listed in the table below (n.d. means not determined). The values reported in the table below are subject to error margins associated with the assay used and the equipment.

Co. No.	Enzymatic hOGA; pIC_{50}	Enzymatic E_{max} (%)	Cellular hOGA; pEC_{50}	Cellular E_{max} (%)
1	8.29	101	7.34	81
2	8.22	99	7.02	87
3	7.59	101	6.13	57
4	8.47	98	7.26	101
5	6.92	91	6.35	67
6	7.72	99	6.54	60
7	8.16	102	6.43	66
8	8.26	97	7.57	98
9	8.17	99	7.23	82
10	8.03	100	7	100
11	8.00	99	6.68	62
12	7.97	101	7.33	88
13	7.86	98	7.16	113
14	7.85	100	6.37	75
15	7.85	98	6.69	64
16	7.87	101	6.5	66
17	7.79	99	6.5	77
18	7.79	99	6.2	56
19	7.7	98	6.27	62
20	7.73	98	6.77	83
21	7.51	95	6.91	69
22	7.38	98	<6	31
23	7.34	99	5.99	51
24	7.34	96	6.4	82
25	6.87	96	<6	29

Co. No.	Enzymatic hOGA; pIC_{50}	Enzymatic E_{max} (%)	Cellular hOGA; pEC_{50}	Cellular E_{max} (%)
26	6.72	98	<6	8
27	6.43	89	<6	18
28	6.32	85	<6	22
29	6	100	<6.7	2
30	5.23	55	<6	12
31	7.06	104	<6	36
32	6.76	100	<6	34
33	7.69	97	6.32	63
34	7.44	99	6.25	54
35	6.75	96	<6	25
36	7.53	101	6.22	55
37	<5	2	<6	8
38	6.04	90	<6	6
39	6.2	94	<6	12
40	6.98	102	<6	27
41	7.55	95	<6	44
42	7.66	93	6.53	70
43	7.83	99	6.36	65
44	7.56	99	6.34	64
45	7.63	94	6.26	94
46	7.87	92	6.33	69
47	7.87	97	7.17	110
48	5.55	66	N/A	N/A
49	7.03	95	6.19	57
50	6.9	94	6.03	48
51	5.83	82	<6	15
52	8.09	102	6.86	73
53	8.14	103	6.87	87
54	N/A	N/A	N/A	N/A
55	N/A	N/A	N/A	N/A
56	N/A	N/A	N/A	N/A
57	7.27	99	6.29	62
58	6.28	95	N/A	N/A
59	8.04	101	6.7	72
60	6.93	100	6.03	44
61	8.03	98	6.97	87

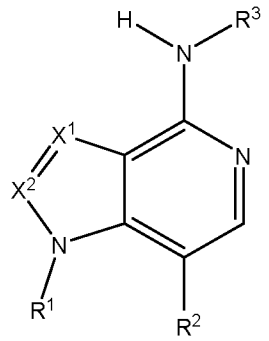
Co. No.	Enzymatic hOGA; pIC_{50}	Enzymatic E_{max} (%)	Cellular hOGA; pEC_{50}	Cellular E_{max} (%)
62	6.16	91	<6	13
63	8.03	98	7.05	100
64	7.37	101	6.63	78
65	6.76	97	<6	24
66	7.07	104	<6	45
67	6.29	94	<6	6
68	5.12	61		
69	6.14	80	<6	6
70	<5	7	<6	7
71	<5	6	<6	27
72	6.26	92	<6	2
73	6.77	100	<6	42
74	5.64	83	<6	6
75	6.28	97	<6	22
76	n.d.			
77	7.23	103	6.37	67
78	n.d.			
79	n.d.			
80	8.05	104	6.7	94
81	7.16	100	6.27	66
82	6.76	97		
83	n.d.			

Representative compounds of the invention were tested according to the procedure as described above, with results as listed in the table below (n.d. means not determined). The values reported in the table below are subject to typical error margins, and are averaged values over several runs of a particular compound, that were obtained after recalibration of the equipment.

Co. No.	Enzymatic hOGA; pIC_{50}	Cellular hOGA; pEC_{50}
69	n.d.	6.14
70	n.d.	<6
71	n.d.	<6
72	n.d.	<6
73	6.91	6.42
74	n.d.	<6
78	7.67	6.37
79	6.6	<6
81	n.d.	6.82
82	6.77	<6
83	5.93	<6

CLAIMS

1. A compound of Formula (I)



(I),

or a tautomer or a stereoisomeric form thereof, or a deuterated form thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of C_{1-6}alkyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, -C(=O)NR^xR^y, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents, wherein the 5-or 6-membered heteroaryl is optionally substituted with one or two independently selected C_{1-4}alkyl substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

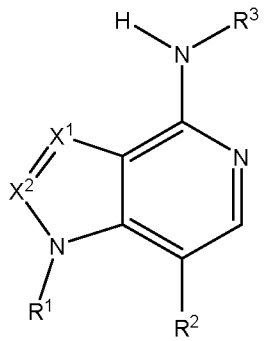
(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy;

or a pharmaceutically acceptable salt, or a solvate thereof; for use as a medicament.

2. A compound of Formula (I)



(I),

or a tautomer or a stereoisomeric form thereof, or a deuterated form thereof, wherein

X^1 and X^2 are each independently selected from CR^4 and N, with the proviso that one of X^1 or X^2 is N;

R^1 is selected from the group consisting of unsubstituted C_{2-6}alkyl; C_{1-6}alkyl substituted with one or more substituents, each independently selected from the group consisting of halo, -CN, -OC_{1-4}alkyl, OH, -C(=O)NR^xR^y, a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl,

triazolyl, pyridyl and pyrimidinyl, and C_{3-6}cycloalkyl optionally substituted with one or more independently selected halo substituents, wherein the 5-or 6-membered heteroaryl is optionally substituted with one or two independently selected C_{1-4}alkyl substituents; C_{1-6}alkyl substituted with oxetanyl, C_{1-6}alkyl wherein two geminal hydrogens are replaced by oxetanylidene; tetrahydropyranyl; and a 5- or 6-membered heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyridyl and pyrimidinyl, each of which may be optionally substituted with or two substituents each independently selected from the group consisting of halo and C_{1-4}alkyl;

with the proviso that a -OC_{1-4}alkyl or -OH substituent, when present, is at least two carbon atoms away from the nitrogen atom of the bicyclic core; wherein

R^x and R^y are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, and C_{3-6}cycloalkyl; or R^x and R^y together with the nitrogen atom to which they are attached form a heterocyclyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl;

R^2 and R^4 when present, are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 is selected from the group consisting of

(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) a 9- to 10-membered bicyclic heteroaryl radical selected from the group consisting of 1H-indazolyl, 1H-benzo[d]imidazolyl, 1,8-naphthyridinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-b]pyridazinyl, indolizinyl, 1H-indolyl, quinolinyl, isoquinolinyl, and thiazolo[4,5-b]pyridinyl; optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, C_{1-4}alkyloxy;

or a pharmaceutically acceptable salt, or a solvate thereof.

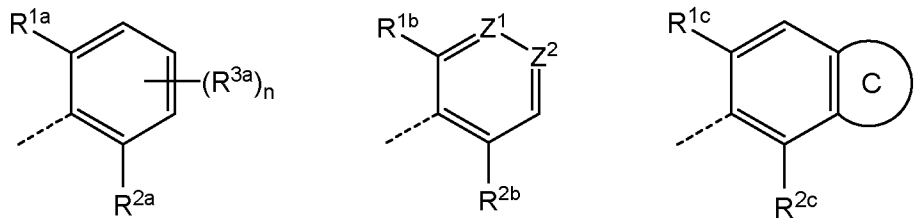
3. The compound according to claim 2, wherein R^3 is selected from the group consisting of

(a) a 5- or 6-membered monocyclic aryl or heteroaryl radical selected from the group consisting of pyrazolyl, phenyl and pyridyl; each of which is substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; and wherein at least one substituent is positioned at the carbon atom ortho- to the NH linker binding R^4 to the bicyclic core; or

(b) 1H-indazolyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het;

wherein Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, and C_{1-4}alkyloxy.

4. The compound according to claim 2 or 3, wherein R^3 is selected from the group consisting of (a), (b), and (c):



(a) (b) (c)

wherein R^{1a}, R^{2a}, R^{1b} and R^{2b} are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; with the proviso that at least one of R^{1a} or R^{2a}, and at least one of R^{1b} or R^{2b} is not hydrogen;

Z^1 and Z^2 are each independently selected from N, CH or CR^{3b}, with the proviso that at least one of Z^1 or Z^2 is N;

R^{3a} and R^{3b} when present, are each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, -(C=O)C_{1-4}alkyl, and Het; wherein

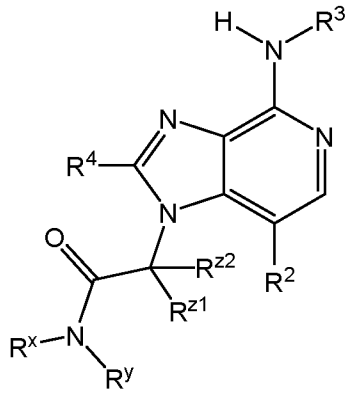
n represents 0, 1 or 2;

Het is selected from the group consisting of pyrazolyl, phenyl, pyridyl optionally substituted with one or more substituents, each independently selected from the group consisting of halo, C_{1-4}alkyl, -CN, and C_{1-4}alkyloxy;

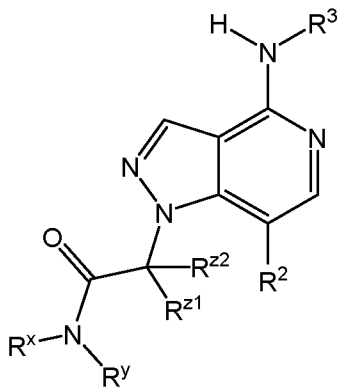
R^{1c} and R^{2c} are each independently selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -CN, monohaloC_{1-4}alkyl, polyhaloC_{1-4}alkyl, C_{1-4}alkyloxy, monohaloC_{1-4}alkyloxy, polyhaloC_{1-4}alkyloxy, and -(C=O)C_{1-4}alkyl; and

C forms a fused 5-membered heteroaromatic ring selected from the group consisting of pyrazolyl, and imidazolyl, each being optionally substituted with one or more independently selected C_{1-4}alkyl substituents.

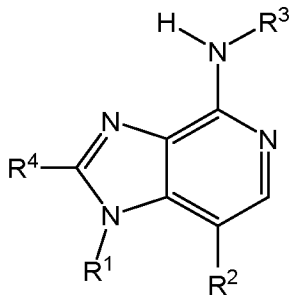
5. The compound according to any one of claims 2 to 4, wherein the compound of Formula (I) has the Formula (I-A), (I-B), (I-C) or (I-D)



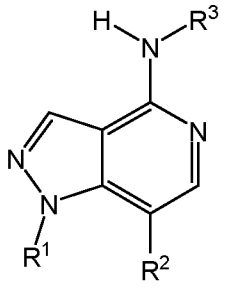
(I-A)



(I-B)



(I-C)



(I-D)

wherein z1 and z2 are each independently selected from hydrogen, deuterium and halogen and the rest of the variables are as defined in any one of claims 2 to 4.

6. A pharmaceutical composition comprising a prophylactically or a therapeutically effective amount of a compound according to any one of claims 2 to 5 and a pharmaceutically acceptable carrier.

7. A process for preparing the pharmaceutical composition according to claim 6, comprising mixing a pharmaceutically acceptable carrier with a prophylactically or a therapeutically effective amount of a compound according to any one of claims 2 to 5.

8. The compound as defined in any one of claims 2 to 5, or the pharmaceutical composition as defined in claim 6, for use as a medicament.

9. The compound for use according to claim 1, in the treatment or prevention of a tauopathy, or an alpha synucleinopathy.

10. The compound as defined in any one of claims 2 to 5, or the pharmaceutical composition as defined in claim 6, for use in the treatment or prevention of a tauopathy, or an alpha synucleinopathy.

11. The compound or the pharmaceutical composition for use according to claim 9 or 10, wherein the tauopathy is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis and parkinsonism-dementia complex, argyrophilic grain disease, chronic traumatic encephalopathy, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by MAPT mutations), Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations), Gerstmann-Sträussler-Scheinker disease, Parkinson's disease, Guadeloupean parkinsonism, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, and white matter tauopathy with globular glial inclusions; and the alpha synucleinopathy is selected from the group consisting of Parkinson's disease, dementia due to Parkinson's (or neurocognitive

disorder due to Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, and alpha synucleinopathy caused by Gaucher's disease.

12. The compound for use according to claim 1, in the control or reduction of the risk of preclinical Alzheimer's disease, prodromal Alzheimer's disease, or tau-related neurodegeneration as observed in different forms of tauopathies.

13. The compound as defined in any one of claims 2 to 5, or the pharmaceutical composition as defined in claim 6, for use in the control or reduction of the risk of preclinical Alzheimer's disease, prodromal Alzheimer's disease, or tau-related neurodegeneration as observed in different forms of tauopathies.

14. The compound for use as defined in claim, in the control or reduction of the risk of prodromal Parkinson's disease.

15. The compound as defined in any one of claims 2 to 5, or the pharmaceutical composition as defined in claim 6, for use in the control or reduction of the risk of prodromal Parkinson's disease.

16. A method of preventing or treating a disorder selected from the group consisting of tauopathy or an alpha synucleinopathy, in particular a tauopathy selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis and parkinsonism-dementia complex, argyrophilic grain disease, chronic traumatic encephalopathy, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by MAPT mutations), Frontotemporal lobar degeneration (some cases caused by C9ORF72 mutations), Gerstmann-Sträussler-Scheinker disease, Parkinson's disease, Guadeloupean parkinsonism, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, and white matter tauopathy with globular glial inclusions, or in particular an alpha synucleinopathy selected from the group consisting of Parkinson's disease, dementia due to Parkinson's (or neurocognitive disorder due to

Parkinson's disease), dementia with Lewy bodies, multiple system atrophy, and alpha synucleinopathy caused by Gaucher's disease, comprising administering to a subject in need thereof, a prophylactically or a therapeutically effective amount of a compound according to any one of claims 2 to 4 or the pharmaceutical composition according to claim 6.