

4,4A,5,7,8,8A-HEXAPYRIDO[4,3-B][1,4]OXAZIN-3-ONE COMPOUNDS AS MAGL INHIBITORS

Field of the Invention

The present invention relates to organic compounds useful for therapy or prophylaxis in a mammal, and in particular to monoacylglycerol lipase (MAGL) inhibitors for the treatment
5 or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, inflammatory bowel disease, abdominal pain, abdominal pain associated with irritable bowel syndrome and/or visceral pain in a mammal.

Background of the Invention

Endocannabinoids (ECs) are signaling lipids that exert their biological actions by interacting with cannabinoid receptors (CBRs), CB1 and CB2. They modulate multiple physiological processes including neuroinflammation, neurodegeneration and tissue regeneration (Iannotti, F.A., *et al.*, *Progress in lipid research* **2016**, 62, 107-28.). In the
15 brain, the main endocannabinoid, 2-arachidonoylglycerol (2-AG), is produced by diacylglycerol lipases (DAGL) and hydrolyzed by the monoacylglycerol lipase, MAGL. MAGL hydrolyses 85% of 2-AG; the remaining 15% being hydrolysed by ABHD6 and ABDH12 (Nomura, D.K., *et al.*, *Science* **2011**, 334, 809.). MAGL is expressed throughout the brain and in most brain cell types, including neurons, astrocytes, oligodendrocytes and
20 microglia cells (Chanda, P.K., *et al.*, *Molecular pharmacology* **2010**, 78, 996; Viader, A., *et al.*, *Cell reports* **2015**, 12, 798.). 2-AG hydrolysis results in the formation of arachidonic acid (AA), the precursor of prostaglandins (PGs) and leukotrienes (LTs). Oxidative metabolism of AA is increased in inflamed tissues. There are two principal enzyme pathways of arachidonic acid oxygenation involved in inflammatory processes, the cyclo-
25 oxygenase which produces PGs and the 5-lipoxygenase which produces LTs. Of the various cyclooxygenase products formed during inflammation, PGE2 is one of the most

- 2 -

important. These products have been detected at sites of inflammation, e.g. in the cerebrospinal fluid of patients suffering from neurodegenerative disorders and are believed to contribute to inflammatory response and disease progression. Mice lacking MAGL (Mgll^{-/-}) exhibit dramatically reduced 2-AG hydrolase activity and elevated 2-AG levels
5 in the nervous system while other arachidonoyl-containing phospho- and neutral lipid species including anandamide (AEA), as well as other free fatty acids, are unaltered. Conversely, levels of AA and AA-derived prostaglandins and other eicosanoids, including prostaglandin E2 (PGE2), D2 (PGD2), F2 (PGF2), and thromboxane B2 (TXB2), are strongly decreased. Phospholipase A₂ (PLA₂) enzymes have been viewed as the principal
10 source of AA, but cPLA₂-deficient mice have unaltered AA levels in their brain, reinforcing the key role of MAGL in the brain for AA production and regulation of the brain inflammatory process.

Neuroinflammation is a common pathological change characteristic of diseases of the brain including, but not restricted to, neurodegenerative diseases (e.g. multiple sclerosis,
15 Alzheimer's disease, Parkinson disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy and mental disorders such as anxiety and migraine). In the brain, production of eicosanoids and prostaglandins controls the neuroinflammation process. The pro-inflammatory agent lipopolysaccharide (LPS) produces a robust, time-dependent increase in brain eicosanoids that is markedly blunted in Mgll^{-/-} mice. LPS
20 treatment also induces a widespread elevation in pro-inflammatory cytokines including interleukin-1-a (IL-1-a), IL-1b, IL-6, and tumor necrosis factor-a (TNF-a) that is prevented in Mgll^{-/-} mice.

Neuroinflammation is characterized by the activation of the innate immune cells of the central nervous system, the microglia and the astrocytes. It has been reported that anti-
25 inflammatory drugs can suppress in preclinical models the activation of glia cells and the progression of disease including Alzheimer's disease and multiple sclerosis (Lleo A., *Cell Mol Life Sci.* **2007**, 64, 1403.). Importantly, genetic and/or pharmacological disruption of MAGL activity also blocks LPS-induced activation of microglial cells in the brain (Nomura, D.K., *et al.*, *Science* **2011**, 334, 809.).

30 In addition, genetic and/or pharmacological disruption of MAGL activity was shown to be protective in several animal models of neurodegeneration including, but not restricted to, Alzheimer's disease, Parkinson's disease and multiple sclerosis. For example, an

- 3 -

irreversible MAGL inhibitor has been widely used in preclinical models of neuroinflammation and neurodegeneration (Long, J.Z., *et al.*, *Nature chemical biology* **2009**, 5, 37.). Systemic injection of such inhibitor recapitulates the Mgl1-/- mice phenotype in the brain, including an increase in 2-AG levels, a reduction in AA levels and related
5 eicosanoids production, as well as the prevention of cytokines production and microglia activation following LPS-induced neuroinflammation (Nomura, D.K., *et al.*, *Science* **2011**, 334, 809.), altogether confirming that MAGL is a druggable target.

Consecutive to the genetic and/or pharmacological disruption of MAGL activity, the endogenous levels of the MAGL natural substrate in the brain, 2-AG, are increased. 2-AG
10 has been reported to show beneficial effects on pain with, for example, anti-nociceptive effects in mice (Ignatowska-Jankowska B. *et al.*, *J. Pharmacol. Exp. Ther.* **2015**, 353, 424.) and on mental disorders, such as depression in chronic stress models (Zhong P. *et al.*, *Neuropsychopharmacology* **2014**, 39, 1763.).

Furthermore, oligodendrocytes (OLs), the myelinating cells of the central nervous system,
15 and their precursors (OPCs) express the cannabinoid receptor 2 (CB2) on their membrane. 2-AG is the endogenous ligand of CB1 and CB2 receptors. It has been reported that both cannabinoids and pharmacological inhibition of MAGL attenuate OLs's and OPCs's vulnerability to excitotoxic insults and therefore may be neuroprotective (Bernal-Chico, A., *et al.*, *Glia* **2015**, 63, 163.). Additionally, pharmacological inhibition of MAGL
20 increases the number of myelinating OLs in the brain of mice, suggesting that MAGL inhibition may promote differentiation of OPCs in myelinating OLs in vivo (Alpar, A., *et al.*, *Nature communications* **2014**, 5, 4421.). Inhibition of MAGL was also shown to promote remyelination and functional recovery in a mouse model of progressive multiple sclerosis (Feliu A. *et al.*, *Journal of Neuroscience* **2017**, 37 (35), 8385.).

25 In addition, in recent years, metabolism is talked highly important in cancer research, especially the lipid metabolism. Researchers believe that the de novo fatty acid synthesis plays an important role in tumor development. Many studies illustrated that endocannabinoids have anti-tumorigenic actions, including anti-proliferation, apoptosis induction and anti-metastatic effects. MAGL as an important decomposing enzyme for
30 both lipid metabolism and the endocannabinoids system, additionally as a part of a gene expression signature, contributes to different aspects of tumourigenesis, including in glioblastoma (Qin, H., *et al.*, *Cell Biochem. Biophys.* **2014**, 70, 33; Nomura DK *et al.*, *Cell*

- 4 -

2009, 140(1), 49-61; Nomura DK *et al.*, *Chem. Biol.* **2011**, 18(7), 846-856, Jinlong Yin *et al.*, *Nature Communications* **2020**, 11, 2978).

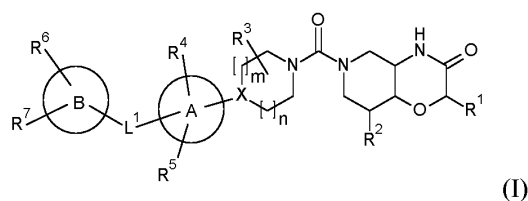
The endocannabinoid system is also involved in many gastrointestinal physiological and physiopathological actions (Marquez, Suarez *et al.* 2009). All these effects are driven
5 mainly via cannabinoid receptors (CBRs), CB1 and CB2. CB1 receptors are present throughout the GI tract of animals and healthy humans, especially in the enteric nervous system (ENS) and the epithelial lining, as well as smooth muscle cells of blood vessels in the colonic wall (Wright, Rooney *et al.* 2005), (Duncan, Davison *et al.* 2005). Activation of CB1 produces anti-emetic, anti-motility, and anti-inflammatory effect, and help to
10 modulate pain (Perisetti, Rimu *et al.* 2020). CB2 receptors are expressed in immune cells such as plasma cells and macrophages, in the lamina propria of the GI tract (Wright, Rooney *et al.* 2005), and primarily on the epithelium of human colonic tissue associated with inflammatory bowel disease (IBD). Activation of CB2 exerts anti-inflammatory effect by reducing pro-inflammatory cytokines. Expression of MAGL is increased in
15 colonic tissue in UC patients (Marquez, Suarez *et al.* 2009) and 2-AG levels are increased in plasma of IBD patients (Grill, Hogenauer *et al.* 2019). Several animal studies have demonstrated the potential of MAGL inhibitors for symptomatic treatment of IBD. MAGL inhibition prevents TNBS-induced mouse colitis and decreases local and circulating inflammatory markers via a CB1/CB2 MoA (Marquez, Suarez *et al.* 2009). Furthermore,
20 MAGL inhibition improves gut wall integrity and intestinal permeability via a CB1 driven MoA (Wang, Zhang *et al.* 2020).

In conclusion, suppressing the action and/or the activation of MAGL is a promising new therapeutic strategy for the treatment or prevention of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders, inflammatory bowel disease,
25 abdominal pain and abdominal pain associated with irritable bowel syndrome. Furthermore, suppressing the action and/or the activation of MAGL is a promising new therapeutic strategy for providing neuroprotection and myelin regeneration. Accordingly, there is a high unmet medical need for new MAGL inhibitors.

Summary of the Invention

30 In a first aspect, the present invention provides compounds of formula (I)

- 5 -

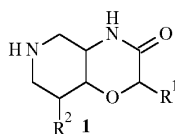


wherein A, B, L¹, X, m, n, and R¹ to R⁷ are as defined herein.

In a further aspect, the present invention provides a process of manufacturing the compounds of formula (I) as described herein, or pharmaceutically acceptable salts

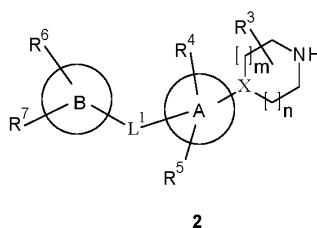
5 thereof, comprising:

reacting 4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-ones **1**, wherein R¹ and R² are as defined herein,



with a heterocyclic amine **2**, wherein A, B, L¹, X, m, n, and R³ to R⁷ are as defined

10 herein



in the presence of a base and a urea forming reagent,
to form said compounds of formula (I) or pharmaceutically acceptable salts thereof.

15 In a further aspect, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, when manufactured according to the processes described herein.

In a further aspect, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance.

- 6 -

In a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier.

In a further aspect, the present invention provides a compound of formula (I) as described
5 herein, or a pharmaceutically acceptable salt thereof, for use in a method of inhibiting monoacylglycerol lipase in a mammal.

In a further aspect, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental
10 disorders in a mammal.

In a further aspect, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine,
15 depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal.

Detailed Description of the Invention

Definitions

20 Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein, unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or
25 process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel
30 combination, of the steps of any method or process so disclosed.

- 7 -

The term “alkyl” refers to a mono- or multivalent, e.g., a mono- or bivalent, linear or branched saturated hydrocarbon group of 1 to 12 carbon atoms. In some preferred embodiments, the alkyl group contains 1 to 6 carbon atoms (“C₁₋₆-alkyl”), e.g., 1, 2, 3, 4, 5, or 6 carbon atoms. In other embodiments, the alkyl group contains 1 to 3 carbon atoms, e.g., 1, 2 or 3 carbon atoms. Some non-limiting examples of alkyl include methyl, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, tert-butyl, and 2,2-dimethylpropyl. Particularly preferred, yet non-limiting examples of alkyl are methyl and 2,2-dimethylpropyl.

The term “alkoxy” refers to an alkyl group, as previously defined, attached to the parent molecular moiety via an oxygen atom. Unless otherwise specified, the alkoxy group contains 1 to 12 carbon atoms. In some preferred embodiments, the alkoxy group contains 1 to 6 carbon atoms (“C₁₋₆-alkoxy”). In other embodiments, the alkoxy group contains 1 to 4 carbon atoms. In still other embodiments, the alkoxy group contains 1 to 3 carbon atoms. Some non-limiting examples of alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy. A particularly preferred, yet non-limiting example of alkoxy is methoxy.

The term “halogen” or “halo” refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I). Preferably, the term “halogen” or “halo” refers to fluoro (F), chloro (Cl) or bromo (Br). Particularly preferred, yet non-limiting examples of “halogen” or “halo” are fluoro (F) and chloro (Cl).

The term “cycloalkyl” as used herein refers to a saturated or partly unsaturated monocyclic or bicyclic hydrocarbon group of 3 to 10 ring carbon atoms (“C₃₋₁₀-cycloalkyl”). In some preferred embodiments, the cycloalkyl group is a saturated monocyclic hydrocarbon group of 3 to 8 ring carbon atoms. “Bicyclic cycloalkyl” refers to cycloalkyl moieties consisting of two saturated carbocycles having two carbon atoms in common, i.e., the bridge separating the two rings is either a single bond or a chain of one or two ring atoms, and to spirocyclic moieties, i.e., the two rings are connected via one common ring atom. Preferably, the cycloalkyl group is a saturated monocyclic hydrocarbon group of 3 to 6 ring carbon atoms, e.g., of 3, 4, 5 or 6 carbon atoms. Some non-limiting examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A particularly preferred, yet non-limiting example of cycloalkyl is cyclopropyl.

- 8 -

The term "aryl" refers to a monocyclic, bicyclic, or tricyclic carbocyclic ring system having a total of 6 to 14 ring members ("C₆-C₁₄-aryl"), preferably, 6 to 12 ring members, and more preferably 6 to 10 ring members, and wherein at least one ring in the system is aromatic. Some non-limiting examples of aryl include phenyl and 9H-fluorenyl (e.g. 9H-
5 fluoren-9-yl). A particularly preferred, yet non-limiting example of aryl is phenyl.

The term "heteroaryl" refers to a mono- or multivalent, monocyclic, bicyclic or tricyclic, preferably bicyclic ring system having a total of 5 to 14 ring members, preferably, 5 to 12 ring members, and more preferably 5 to 10 ring members, wherein at least one ring in the system is aromatic, and at least one ring in the system contains one or more heteroatoms.
10 Preferably, "heteroaryl" refers to a 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N. Most preferably, "heteroaryl" refers to a 5-10 membered heteroaryl comprising 1 to 2 heteroatoms independently selected from O, S and N. Some non-limiting examples of heteroaryl include spiro[cyclopropane-1,3'-indoline] (e.g., spiro[cyclopropane-1,3'-indoline]-1'-yl), 2-pyridyl, 3-pyridyl, 4-pyridyl,
15 indol-1-yl, 1H-indol-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indol-7-yl, 1,2-benzoxazol-3-yl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl, 1,2-benzoxazol-6-yl, 1,2-benzoxazol-7-yl, 1H-indazol-3-yl, 1H-indazol-4-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1H-indazol-7-yl, pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, imidazol-1-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl,
20 oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, pyridazin-3-yl, and pyridazin-4-yl. Particularly preferred, yet non-limiting examples of heteroaryl are oxadiazolyl, pyridazinyl, pyridyl, and thiazolyl.

The term "hydroxy" refers to an -OH group.

25 The term "cyano" refers to a -CN (nitrile) group.

The term "amino" refers to an -NH₂ group.

The term "alkylsulfonyl" refers to a group alkyl-SO₂-.

The term "carbamoyl" refers to a group H₂N-C(O)-.

The term "cycloalkylalkoxy" refers to an alkoxy group, wherein at least one of the
30 hydrogen atoms of the alkoxy group has been replaced by a cycloalkyl group. Preferably,

- 9 -

“cycloalkylalkoxy” refers to an alkoxy group wherein 1, 2 or 3 hydrogen atoms, most preferably 1 hydrogen atom of the alkoxy group have been replaced by a cycloalkyl group. A particularly preferred, yet non-limiting example of cycloalkylalkoxy is cyclopropylmethoxy.

- 5 The term “haloalkyl” refers to an alkyl group, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a halogen atom, preferably fluoro. Preferably, “haloalkyl” refers to an alkyl group wherein 1, 2 or 3 hydrogen atoms of the alkyl group have been replaced by a halogen atom, most preferably fluoro. Particularly preferred, yet non-limiting examples of haloalkyl are trifluoromethyl and trifluoroethyl.
- 10 The term “haloalkoxy” refers to an alkoxy group, wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by a halogen atom, preferably fluoro. Preferably, “haloalkoxy” refers to an alkoxy group wherein 1, 2 or 3 hydrogen atoms of the alkoxy group have been replaced by a halogen atom, most preferably fluoro. A particularly preferred, yet non-limiting example of haloalkoxy is trifluoromethoxy (–
- 15 OCF₃).

The term “cycloalkylalkoxy” refers to an alkoxy group, wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by a cycloalkyl group. Preferably, “cycloalkylalkoxy” refers to an alkoxy group wherein 1, 2 or 3 hydrogen atoms, most preferably 1 hydrogen atom of the alkoxy group have been replaced by a cycloalkyl group.

- 20 A particularly preferred, yet non-limiting example of cycloalkylalkoxy is cyclopropylmethoxy.

The term “hydroxyalkyl” refers to an alkyl group, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a hydroxy group. Preferably, “hydroxyalkyl” refers to an alkyl group wherein 1, 2 or 3 hydrogen atoms, most preferably

25 1 hydrogen atom of the alkyl group have been replaced by a hydroxy group. Preferred, yet non-limiting examples of hydroxyalkyl are hydroxymethyl and hydroxyethyl (e.g. 2-hydroxyethyl). A particularly preferred, yet non-limiting example of hydroxyalkyl is hydroxymethyl.

- The term “aminoalkoxy” refers to an alkoxy group, wherein at least one of the hydrogen
- 30 atoms of the alkoxy group has been replaced by an amino group. Preferably, “aminoalkoxy” refers to an alkoxy group wherein 1, 2 or 3 hydrogen atoms, most

- 10 -

preferably 1 hydrogen atom of the alkoxy group have been replaced by an amino group. Preferred, yet non-limiting examples of aminoalkoxy are aminomethoxy and aminoethoxy (e.g. 2-aminoethoxy).

The term "pharmaceutically acceptable salt" refers to those salts which retain the
5 biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, in particular hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric
10 acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein and the like. In addition these salts may be prepared by addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts
15 derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyimine resins and the like. Particular pharmaceutically
20 acceptable salts of compounds of formula (I) are hydrochloride salts.

The term "protective group" (PG) denotes the group which selectively blocks a reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site in the meaning conventionally associated with it in synthetic chemistry. Protective groups can be removed at the appropriate point.
25 Exemplary protective groups are amino-protective groups, carboxy-protective groups or hydroxy-protective groups. Particular protective groups are the tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), fluorenylmethoxycarbonyl (Fmoc) and benzyl (Bn). Further particular protective groups are the tert-butoxycarbonyl (Boc) and the fluorenylmethoxycarbonyl (Fmoc). More particular protective group is the tert-
30 butoxycarbonyl (Boc). Exemplary protective groups and their application in organic synthesis are described, for example, in "Protective Groups in Organic Chemistry" by T. W. Greene and P. G. M. Wuts, 5th Ed., 2014, John Wiley & Sons, N.Y.

- 11 -

The term “urea forming reagent” refers to a chemical compound that is able to render a first amine to a species that will react with a second amine, thereby forming an urea derivative. Non-limiting examples of a urea forming reagent include bis(trichloromethyl) carbonate, phosgene, trichloromethyl chloroformate, (4-nitrophenyl)carbonate, 1,1'-
5 carbonyl-di-(1,2,4-triazole), and 1,1'-carbonyldiimidazole. The urea forming reagents described in G. Sartori et al., *Green Chemistry* **2000**, 2, 140 are incorporated herein by reference.

The compounds of formula (I) can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example,
10 racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

According to the Cahn-Ingold-Prelog Convention, the asymmetric carbon atom can be of the "R" or "S" configuration.

The abbreviation “MAGL” refers to the enzyme monoacylglycerol lipase. The terms
15 “MAGL” and “monoacylglycerol lipase” are used herein interchangeably.

The term “treatment” as used herein includes: (1) inhibiting the state, disorder or condition (e.g. arresting, reducing or delaying the development of the disease, or a relapse thereof in case of maintenance treatment, of at least one clinical or subclinical symptom thereof); and/or (2) relieving the condition (i.e., causing regression of the state, disorder or
20 condition or at least one of its clinical or subclinical symptoms). The benefit to a patient to be treated is either statistically significant or at least perceptible to the patient or to the physician. However, it will be appreciated that when a medicament is administered to a patient to treat a disease, the outcome may not always be effective treatment.

The term “prophylaxis” as used herein includes: preventing or delaying the appearance of
25 clinical symptoms of the state, disorder or condition developing in a mammal and especially a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition.

The term “neuroinflammation” as used herein relates to acute and chronic inflammation of
30 the nervous tissue, which is the main tissue component of the two parts of the nervous

- 12 -

system; the brain and spinal cord of the central nervous system (CNS), and the branching peripheral nerves of the peripheral nervous system (PNS). Chronic neuroinflammation is associated with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. Acute neuroinflammation usually follows injury to the
5 central nervous system immediately, e.g., as a result of traumatic brain injury (TBI).

The term "traumatic brain injury" ("TBI", also known as "intracranial injury"), relates to damage to the brain resulting from external mechanical force, such as rapid acceleration or deceleration, impact, blast waves, or penetration by a projectile.

The term "neurodegenerative diseases" relates to diseases that are related to the
10 progressive loss of structure or function of neurons, including death of neurons. Examples of neurodegenerative diseases include, but are not limited to, multiple sclerosis, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.

The term "mental disorders" (also called mental illnesses or psychiatric disorders) relates to behavioral or mental patterns that may cause suffering or a poor ability to function in
15 life. Such features may be persistent, relapsing and remitting, or occur as a single episode. Examples of mental disorders include, but are not limited to, anxiety and depression.

The term "pain" relates to an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Examples of pain include, but are not limited to, nociceptive pain, chronic pain (including idiopathic pain), neuropathic pain including
20 chemotherapy induced neuropathy, phantom pain and psychogenic pain. A particular example of pain is neuropathic pain, which is caused by damage or disease affecting any part of the nervous system involved in bodily feelings (i.e., the somatosensory system). In one embodiment, "pain" is neuropathic pain resulting from amputation or thoracotomy. In one embodiment, "pain" is chemotherapy induced neuropathy.

25 The term "neurotoxicity" relates to toxicity in the nervous system. It occurs when exposure to natural or artificial toxic substances (neurotoxins) alter the normal activity of the nervous system in such a way as to cause damage to nervous tissue. Examples of neurotoxicity include, but are not limited to, neurotoxicity resulting from exposure to substances used in chemotherapy, radiation treatment, drug therapies, drug abuse, and
30 organ transplants, as well as exposure to heavy metals, certain foods and food additives,

pesticides, industrial and/or cleaning solvents, cosmetics, and some naturally occurring substances.

The term “cancer” refers to a disease characterized by the presence of a neoplasm or tumor resulting from abnormal uncontrolled growth of cells (such cells being "cancer cells"). As

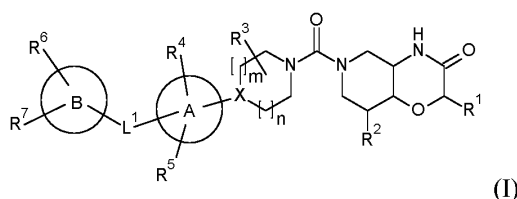
5 used herein, the term cancer explicitly includes, but is not limited to, hepatocellular carcinoma, colon carcinogenesis and ovarian cancer.

The term “mammal” as used herein includes both humans and non-humans and includes but is not limited to humans, non-human primates, canines, felines, murines, bovines, equines, and porcines. In a particularly preferred embodiment, the term “mammal” refers

10 to humans.

Compounds of the Invention

In a first aspect (A1), the present invention provides compounds of Formula (I)



or pharmaceutically acceptable salts thereof, wherein:

15 A is selected from C₆-C₁₄-aryl, 5- to 14-membered heteroaryl and 3- to 14-membered heterocyclyl;

B is

(i) C₆-C₁₄-aryl; and L¹ is -O-; or

(ii) 5- to 14-membered heteroaryl; and L^1 is a covalent bond or $-O-$;

20 m is 0, n is 0 or 1 and X is $\mathbb{C}R^8$; or

m is 1, n is 1 or 2 and X is $\mathbb{C}R^8$ or N ;

R¹, R², and R³ are independently selected from hydrogen and C₁₋₆-alkyl;

R⁴, R⁵, R⁶ and R⁷ are independently selected from hydrogen, halogen, cyano,

hydroxy, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, amino-C₁₋₆-alkoxy, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₁₋₆-alkylsulfonyl, SF₅, carbamoyl, C₃₋₁₀-cycloalkyl-C₁₋₆-alkoxy-, C₁₋₆-alkyl-NH-C(O)-, C₁₋₆-alkyl-C(O)-NH-, and C₃₋₁₀-cycloalkyl, wherein each C₃₋₁₀-cycloalkyl is optionally substituted with 1-2 substituents selected from C₁₋₆-alkyl and halo-C₁₋₆-alkyl; and

- 14 -

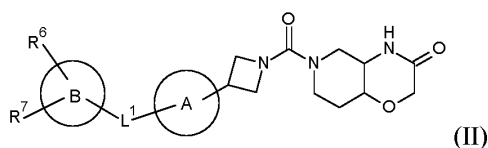
R^8 is selected from hydrogen, halogen, hydroxy, halo- C_{1-6} -alkyl, and C_{1-6} -alkyl.

The invention also provides the following enumerated Embodiments (E) of the first aspect (A1) of the invention:

- 5 E1. The compound of formula (I) according to A1, or a pharmaceutically acceptable salt thereof, wherein A is C_6 - C_{14} -aryl or 5- to 14-membered heteroaryl.
- E2. The compound of formula (I) according to A1, or a pharmaceutically acceptable salt thereof, wherein A is phenyl or pyridyl.
- E3. The compound of formula (I) according to A1, or a pharmaceutically acceptable salt thereof, wherein A is C_6 - C_{14} -aryl.
- 10 E4. The compound of formula (I) according to A1, or a pharmaceutically acceptable salt thereof, wherein A is phenyl.
- E5. The compound of formula (I) according to any one of A1 and E1-E4, or a pharmaceutically acceptable salt thereof, wherein
- B is
- 15 (i) phenyl; and L^1 is $-O-$; or
- (ii) selected from oxadiazolyl, pyridazinyl, pyridyl, and thiazolyl; and L^1 is a covalent bond or $-O-$.
- E6. The compound of formula (I) according to any one of A1 and E1-E5, wherein:
- 20 m is 0, n is 0 and X is CR^8 ; or
- m is 1, n is 1 and X is CR^8 or N.
- E7. The compound of formula (I) according to any one of A1 and E1-E5, wherein m is 0, n is 0 and X is CR^8 .
- E8. The compound of formula (I) according to any one of A1 and E1-E7, wherein R^1 is hydrogen.
- 25 E9. The compound of formula (I) according to any one of A1 and E1-E8, wherein R^2 is hydrogen.
- E10. The compound of formula (I) according to any one of A1 and E1-E9, wherein R^3 is hydrogen.

- 15 -

- E11. The compound of formula (I) according to any one of A1 and E1-E10, wherein R⁴ is hydrogen.
- E12. The compound of formula (I) according to any one of A1 and E1-E11, wherein R⁵ is hydrogen.
- 5 E13. The compound of formula (I) according to any one of A1 and E1-E12, wherein R⁶ is selected from hydrogen, halogen, cyano, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, and C₁₋₆-alkylsulfonyl.
- E14. The compound of formula (I) according to any one of A1 and E1-E12, wherein R⁶ is selected from hydrogen, halogen, cyano, and C₁₋₆-alkyl.
- 10 E15. The compound of formula (I) according to any one of A1 and E1-E12, wherein R⁶ is selected from hydrogen, fluoro, chloro, cyano, methyl, and 2,2-dimethylpropyl.
- E16. The compound of formula (I) according to any one of A1 and E1-E15, wherein R⁷ is selected from hydrogen, halogen, and C₁₋₆-alkyl.
- E17. The compound of formula (I) according to any one of A1 and E1-E15, wherein R⁷ is
15 selected from hydrogen, fluoro, and methyl.
- E18. The compound of formula (I) according to any one of A1 and E1-E15, wherein R⁷ is hydrogen or halogen.
- E19. The compound of formula (I) according to any one of A1 and E1-E15, wherein R⁷ is hydrogen or fluoro.
- 20 E20. The compound of formula (I) according to any one of A1 and E1-E19, wherein R⁸ is hydrogen or hydroxy.
- E21. The compound of formula (I) according to any one of A1 and E1-E19, wherein R⁸ is hydrogen.
- 25 E22. The compound of formula (I) according to A1, wherein the compound of formula (I) is a compound of formula (II), or a pharmaceutically acceptable salt thereof,



- 16 -

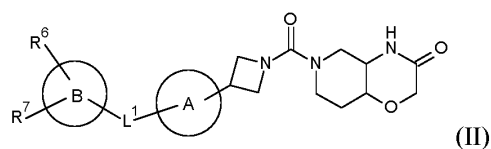
wherein:

A is C₆-C₁₄-aryl;

B is

(i) C₆-C₁₄-aryl; and L¹ is -O-; or5 (ii) 5- to 14-membered heteroaryl; and L¹ is a covalent bond or -O-;R⁶ is selected from hydrogen, halogen, cyano, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, and C₁₋₆-alkylsulfonyl; andR⁷ is selected from hydrogen, halogen, and C₁₋₆-alkyl.

E23. The compound of formula (I) according to A1, wherein the compound of formula (I)
 10 is a compound of formula (II), or a pharmaceutically acceptable salt thereof,



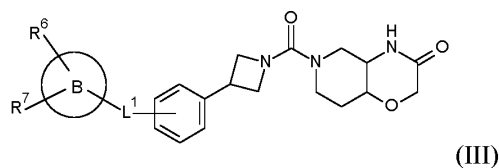
wherein:

A is C₆-C₁₄-aryl;

B is

15 (i) C₆-C₁₄-aryl; and L¹ is -O-; or(ii) 5- to 14-membered heteroaryl; and L¹ is a covalent bond or -O-;R⁶ is selected from hydrogen, halogen, cyano, and C₁₋₆-alkyl; andR⁷ is selected from hydrogen, and halogen.

E24. The compound of formula (I) according to A1, wherein the compound of formula (I)
 20 is a compound of formula (III), or a pharmaceutically acceptable salt thereof,



wherein:

B is

(i) phenyl; and L¹ is -O-; or

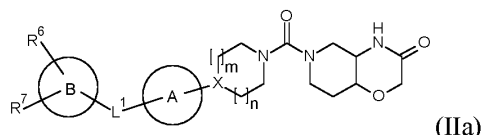
25 (ii) selected from oxadiazolyl, pyridazinyl, pyridyl, and thiazolyl; and L¹ is a covalent bond or -O-;

- 17 -

R^6 is selected from hydrogen, fluoro, chloro, cyano, methyl, and 2,2-dimethylpropyl; and

R^7 is selected from hydrogen, and fluoro.

E25. The compound of formula (I) according to A1, wherein the compound of formula (I) is a compound of formula (IIa), or a pharmaceutically acceptable salt thereof,



wherein:

A is C_6 - C_{14} -aryl or 5- to 14-membered heteroaryl;

B is

(i) C_6 - C_{14} -aryl; and L^1 is $-O-$; or

(ii) 5- to 14-membered heteroaryl; and L^1 is a covalent bond or $-O-$;

m is 0, n is 0 and X is CR^8 ; or

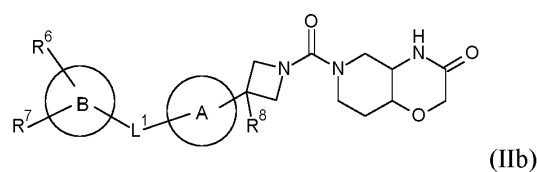
m is 1, n is 1 and X is CR^8 or N;

R^6 is selected from hydrogen, halogen, cyano, C_{1-6} -alkyl, C_{1-6} -alkoxy, halo- C_{1-6} -alkyl, C_{3-10} -cycloalkyl, and C_{1-6} -alkylsulfonyl;

R^7 is selected from hydrogen, halogen, and C_{1-6} -alkyl; and

R^8 is selected from hydrogen and hydroxy.

E26. The compound of formula (I) according to A1, wherein the compound of formula (I) is a compound of formula (IIb), or a pharmaceutically acceptable salt thereof,



wherein:

A is C_6 - C_{14} -aryl or 5- to 14-membered heteroaryl;

B is

(i) C_6 - C_{14} -aryl; and L^1 is $-O-$; or

(ii) 5- to 14-membered heteroaryl; and L^1 is a covalent bond or $-O-$;

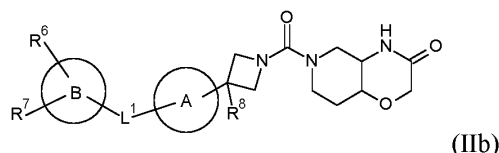
R^6 is selected from hydrogen, halogen, cyano, and C_{1-6} -alkyl;

R^7 is selected from hydrogen, C_{1-6} -alkyl, and halogen; and

- 18 -

R^8 is selected from hydrogen and hydroxy.

E27. The compound of formula (I) according to A1, wherein the compound of formula (I) is a compound of formula (IIb), or a pharmaceutically acceptable salt thereof,



5 wherein:

A is phenyl or pyridyl;

B is

(i) phenyl; and L^1 is $-O-$; or

10 (ii) selected from oxadiazolyl, pyridazinyl, pyridyl, and thiazolyl; and L^1 is a covalent bond or $-O-$;

R^6 is selected from hydrogen, fluoro, chloro, cyano, methyl, and 2,2-dimethylpropyl;

R^7 is selected from hydrogen, methyl, and fluoro; and

R^8 is selected from hydrogen and hydroxy.

15 E28. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , and R^3 are all hydrogen.

E29. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein A is C_6 - C_{14} -aryl and R^4 and R^5 are both hydrogen.

20 E30. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein A is phenyl and R^4 and R^5 are both hydrogen.

E31. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein

25 B is

(i) C_6 - C_{14} -aryl; and L^1 is $-O-$; or

(ii) 5- to 14-membered heteroaryl; and L^1 is a covalent bond or $-O-$;

R^6 is selected from hydrogen, halogen, cyano, C_{1-6} -alkyl, C_{1-6} -alkoxy, halo- C_{1-6} -alkyl, C_{3-10} -cycloalkyl, and C_{1-6} -alkylsulfonyl; and

- 19 -

R^7 is selected from hydrogen, halogen, and C_{1-6} -alkyl.

E32. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein

B is

- 5 (i) C_6 - C_{14} -aryl; and L^1 is $-O-$; or
 (ii) 5- to 14-membered heteroaryl; and L^1 is a covalent bond or $-O-$;

R^6 is selected from hydrogen, halogen, cyano, and C_{1-6} -alkyl; and

R^7 is selected from hydrogen, and halogen.

E33. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein

B is

- (i) phenyl; and L^1 is $-O-$; or
 (ii) oxadiazolyl, pyridazinyl, pyridyl, and thiazolyl; and L^1 is a covalent bond or $-O-$;

15 R^6 is selected from hydrogen, fluoro, chloro, cyano, methyl, and 2,2-dimethylpropyl; and

R^7 is selected from hydrogen, and fluoro.

E34. The compound of formula (I) according to any one of A1 and E1-E33, or a pharmaceutically acceptable salt thereof, selected from:

- 20 (4aR,8aS)-6-(3-(4-Phenoxyphenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
 (4aR,8aS)-6-[3-[4-(2-Chlorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 (4aR,8aS)-6-[3-(4-Pyrimidin-2-yloxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 25 (4aR,8aS)-6-[3-[4-[(2-Methyl-3-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 (4aR,8aS)-6-[3-[4-(4-Methylpyrimidin-2-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 30 (4aR,8aS)-6-[3-(4-Pyridazin-3-yloxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

- (4aR,8aS)-6-[3-[4-[(4-Methyl-3-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-[(5-Fluoro-3-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 5 (4aR,8aS)-6-[3-[4-[(5-Chloro-3-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(3-Pyridyloxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(4-Methylpyridazin-3-yl)oxyphenyl]azetidine-1-carbonyl]-
10 4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(3-Chloropyridazin-4-yl)oxyphenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(4-Methoxypyrimidin-2-yl)oxyphenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 15 (4aR,8aS)-6-[3-[4-[4-(Trifluoromethyl)pyrimidin-2-yl]oxyphenyl]azetidine-1-
carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(3-Fluorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(4-Fluorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
20 hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(2,4-Difluorophenoxy)phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(2-Fluorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 25 (4aR,8aS)-6-[3-[4-(4-Chlorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(3-Chlorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(2-Methylphenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
30 hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-[3-(Trifluoromethyl)phenoxy]phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 2-[4-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-
carbonyl]azetidin-3-yl]phenoxy]benzonitrile;

- (4aR,8aS)-6-[3-[4-(2-Chloropyrimidin-4-yl)oxyphenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (+)-(4aR,8aS)-6-[3-[4-(4-Cyclopropylpyrimidin-2-yl)oxyphenyl]azetidine-1-
carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 5 (4aR,8aS)-6-[3-[4-[(6-Methyl-2-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-[(4-chloro-3-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-[(3-Fluoro-4-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-
10 4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one ;
- (+)-(4aR,8aS)-6-[3-[4-(2-Methylsulfonylpyrimidin-4-yl)oxyphenyl]azetidine-1-
carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one ;
- (4aR,8aS)-6-[3-[4-[(3,6-Dimethyl-2-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 15 (4aR,8aS)-6-[3-[4-(1H-Pyrazol-5-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-[2-(2,2-Dimethylpropyl)pyrazol-3-yl]phenyl]azetidine-1-
carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-[1-(2,2-Dimethylpropyl)pyrazol-3-yl]phenyl]azetidine-1-
20 carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(3-Chloro-2-pyridyl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(2,4-Dimethyloxazol-5-yl)phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 25 (4aR,8aS)-6-[3-[4-(3,5-Dimethylpyrazol-1-yl)phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-[3-(2,2-Dimethylpropyl)triazol-4-yl]phenyl]azetidine-1-
carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-[5-(2,2-Dimethylpropyl)-1,2,4-oxadiazol-3-yl]phenyl]azetidine-1-
30 carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-[5-(2,2-Dimethylpropyl)-1,3,4-oxadiazol-2-yl]phenyl]azetidine-1-
carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-[2-(2-Fluoroethyl)pyrazol-3-yl]phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

- (4aR,8aS)-6-[3-[4-[1-(2-Fluoroethyl)pyrazol-4-yl]phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(4-Methyl-1,3-thiazol-2-yl)phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 5 (4aR,8aS)-6-[3-[4-(1-Methylpyrazol-3-yl)phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(6-Fluoropyridin-3-yl)phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(2-Fluoropyridin-4-yl)phenyl]azetidine-1-carbonyl]-
10 4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(1-Methylpyrazol-4-yl)phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[4-(2-Methylpyrazol-3-yl)phenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 15 (4aR,8aS)-6-[3-[5-(4-Fluorophenoxy)-2-pyridyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-(3-(6-(4-Fluorophenoxy)pyridin-3-yl)azetidine-1-carbonyl)hexahydro-
2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-(6-(4-(Trifluoromethoxy)phenoxy)pyridin-3-yl)azetidine-1-
20 carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-(6-(4-Chlorophenoxy)pyridin-3-yl)azetidine-1-carbonyl)hexahydro-
2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[4-(3,6-Dimethylpyridazin-4-yl)oxyphenyl]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 25 (4aR,8aS)-6-(3-(6-(2-Chlorophenoxy)pyridin-3-yl)azetidine-1-carbonyl)hexahydro-
2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-(6-(3-Chlorophenoxy)pyridin-3-yl)azetidine-1-carbonyl)hexahydro-
2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[4-[4-(4-Fluorophenoxy)phenyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-
30 hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-Hydroxy-3-(4-phenoxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-Hydroxy-3-(5-phenoxy-2-pyridyl)azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(4aR,8aS)-6-[4-(4-Phenoxyphenyl)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and
 (4aR,8aS)-6-[4-(4-Phenoxyphenyl)piperazine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one.

5 E35. The compound of formula (I) according to E34, or a pharmaceutically acceptable salt thereof, selected from:

- (4aR,8aS)-6-(3-(4-Phenoxyphenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
 (4aR,8aS)-6-[3-[4-(3-Chloropyridazin-4-yl)oxyphenyl]azetidine-1-carbonyl]-
 10 4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 (4aR,8aS)-6-[3-[4-(2,4-Difluorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 (4aR,8aS)-6-[3-[4-(2-Fluorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 15 2-[4-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]phenoxy]benzonitrile;
 (4aR,8aS)-6-[3-[4-(3-Chloro-2-pyridyl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 (4aR,8aS)-6-[3-[4-[5-(2,2-Dimethylpropyl)-1,2,4-oxadiazol-3-yl]phenyl]azetidine-1-carbonyl]-
 20 4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 (4aR,8aS)-6-[3-[4-(4-Methyl-1,3-thiazol-2-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 (4aR,8aS)-6-[3-[5-(4-fluorophenoxy)-2-pyridyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 25 (4aR,8aS)-6-[3-[4-(3,6-dimethylpyridazin-4-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 (4aR,8aS)-6-[3-[6-(2-chlorophenoxy)-3-pyridyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and
 (4aR,8aS)-6-[3-hydroxy-3-(4-phenoxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one.
 30

E36. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein R¹ and R² are both hydrogen.

- 24 -

- E37. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein:
R³ is hydrogen;
m is 0, n is 0 and X is CR⁸; or
5 m is 1, n is 1 and X is CR⁸ or N; and
R⁸ is hydrogen or hydroxy.
- E38. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein:
R³ is hydrogen;
10 m is 0, n is 0 and X is CR⁸; and
R⁸ is hydrogen or hydroxy.
- E39. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein:
A is C₆-C₁₄-aryl or 5- to 14-membered heteroaryl;
15 B is
(i) C₆-C₁₄-aryl; and L¹ is -O-; or
(ii) 5- to 14-membered heteroaryl; and L¹ is a covalent bond or -O-;
R⁴ and R⁵ are both hydrogen;
R⁶ is selected from hydrogen, halogen, cyano, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-
20 alkyl, C₃₋₁₀-cycloalkyl, and C₁₋₆-alkylsulfonyl; and
R⁷ is selected from hydrogen, halogen, and C₁₋₆-alkyl.
- E40. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein:
A is C₆-C₁₄-aryl or 5- to 14-membered heteroaryl;
25 B is
(i) C₆-C₁₄-aryl; and L¹ is -O-; or
(ii) 5- to 14-membered heteroaryl; and L¹ is a covalent bond or -O-;
R⁴ and R⁵ are both hydrogen;
R⁶ is selected from hydrogen, halogen, cyano, and C₁₋₆-alkyl; and
30 R⁷ is selected from hydrogen, halogen, and C₁₋₆-alkyl.
- E41. The compound of formula (I) according to any one of A1 and E1-E21, or a pharmaceutically acceptable salt thereof, wherein:

- 25 -

A is phenyl or pyridyl;

B is

(i) phenyl; and L¹ is –O–; or

(ii) selected from oxadiazolyl, pyridazinyl, pyridyl, and thiazolyl; and L¹ is a
5 covalent bond or –O–;

R⁴ and R⁵ are both hydrogen;

R⁶ is selected from hydrogen, fluoro, chloro, cyano, methyl, and 2,2-
dimethylpropyl; and

R⁷ is selected from hydrogen, halogen, and methyl.

10 In a particular embodiment, the present invention provides pharmaceutically acceptable salts of the compounds according to formula (I) as described herein, especially hydrochloride salts. In a further particular embodiment, the present invention provides compounds according to formula (I) as described herein as free bases.

In some embodiments, the compounds of formula (I) are isotopically-labeled by having
15 one or more atoms therein replaced by an atom having a different atomic mass or mass number. Such isotopically-labeled (i.e., radiolabeled) compounds of formula (I) are considered to be within the scope of this disclosure. Examples of isotopes that can be incorporated into the compounds of formula (I) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, and iodine, such as, but not
20 limited to, ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ³¹P, ³²P, ³⁵S, ¹⁸F, ³⁶Cl, ¹²³I, and ¹²⁵I, respectively. Certain isotopically-labeled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ³H, and carbon-14, i.e., ¹⁴C, are particularly useful for this purpose in view of their ease of incorporation and ready means
25 of detection. For example, a compound of formula (I) can be enriched with 1, 2, 5, 10, 25, 50, 75, 90, 95, or 99 percent of a given isotope.

Substitution with heavier isotopes such as deuterium, i.e. ²H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements.

30 Substitution with positron emitting isotopes, such as ¹¹C, ¹⁸F, ¹⁵O and ¹³N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

- 26 -

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

5 Processes of Manufacturing

The preparation of compounds of formula (I) of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the invention are shown in the following general schemes. The skills required for carrying out the reaction and purification of the resulting products are known to those persons skilled in the art. The
10 substituents and indices used in the following description of the processes have the significance given herein, unless indicated to the contrary.

If one of the starting materials, intermediates or compounds of formula (I) contain one or more functional groups which are not stable or are reactive under the reaction conditions of one or more reaction steps, appropriate protective groups (as described e.g., in
15 “Protective Groups in Organic Chemistry” by T. W. Greene and P. G. M. Wutts, 5th Ed., 2014, John Wiley & Sons, N.Y.) can be introduced before the critical step applying methods well known in the art. Such protective groups can be removed at a later stage of the synthesis using standard methods described in the literature.

If starting materials or intermediates contain stereogenic centers, compounds of formula (I)
20 can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art e.g., chiral HPLC, chiral SFC or chiral crystallization. Racemic compounds can e.g., be separated into their antipodes via diastereomeric salts by crystallization with optically pure acids or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbent or a chiral eluent. It is equally
25 possible to separate starting materials and intermediates containing stereogenic centers to afford diastereomerically/enantiomerically enriched starting materials and intermediates. Using such diastereomerically/enantiomerically enriched starting materials and intermediates in the synthesis of compounds of formula (I) will typically lead to the respective diastereomerically/enantiomerically enriched compounds of formula (I).

30 A person skilled in the art will acknowledge that in the synthesis of compounds of formula (I) - insofar not desired otherwise - an “orthogonal protection group strategy” will be

- 27 -

applied, allowing the cleavage of several protective groups one at a time each without affecting other protective groups in the molecule. The principle of orthogonal protection is well known in the art and has also been described in literature (e.g. Barany and R. B. Merrifield, *J. Am. Chem. Soc.* **1977**, 99, 7363; H. Waldmann et al., *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2056).

A person skilled in the art will acknowledge that the sequence of reactions may be varied depending on reactivity and nature of the intermediates.

In more detail, the compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. Also, for reaction conditions described in literature affecting the described reactions see for example: *Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999*). It was found convenient to carry out the reactions in the presence or absence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. The described reactions can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. It is convenient to carry out the described reactions in a temperature range between -78 °C to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 hours to several days will usually suffice to yield the described intermediates and compounds. The reaction sequence is not limited to the one displayed in the schemes, however, depending on the starting materials and their respective reactivity, the sequence of reaction steps can be freely altered.

If starting materials or intermediates are not commercially available or their synthesis not described in literature, they can be prepared in analogy to existing procedures for close analogues or as outlined in the experimental section.

The following abbreviations are used in the present text:

AcOH = acetic acid, ACN = acetonitrile, Bn = benzyl, Boc = tert-butyloxycarbonyl, CAS RN = chemical abstracts registration number, Cbz = benzyloxycarbonyl, Cs₂CO₃ = cesium

- 28 -

carbonate, CO = carbon monoxide, CuCl = copper(I) chloride, CuCN = copper(I) cyanide, CuI = copper(I) iodide, DAST = (diethylamino)sulfur trifluoride, DBU = 1,8-diazabicyclo[5,4,0]undec-7-ene, DEAD = diethyl azodicarboxylate, DIAD = diisopropyl azodicarboxylate, DMAP = 4-dimethylaminopyridine, DME = dimethoxyethane,

5 DMEDA = N,N'-dimethylethylenediamine, DMF = N,N-dimethylformamide, DIPEA = N,N-diisopropylethylamine, dppf = 1,1 bis(diphenyl phosphino)ferrocene, EDC.HCl = N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, EI = electron impact, ESI = electrospray ionization, EtOAc = ethyl acetate, EtOH = ethanol, h = hour(s), FA = formic acid, H₂O = water, H₂SO₄ = sulfuric acid, HATU = 1-[bis(dimethylamino)methylene]-1H-

10 1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate, HBTU = O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate, HCl = hydrogen chloride, HOBt = 1-hydroxy-1H-benzotriazole, HPLC = high performance liquid chromatography, iPrMgCl = isopropylmagnesium chloride, I₂ = iodine, IPA = 2-propanol, ISP = ion spray positive (mode), ISN = ion spray negative (mode), K₂CO₃ = potassium carbonate, KHCO₃ =

15 potassium bicarbonate, KI = potassium iodide, KOH = potassium hydroxide, K₃PO₄ = potassium phosphate tribasic, LiAlH₄ or LAH = lithium aluminium hydride, LiHMDS = lithium bis(trimethylsilyl)amide, LiOH = lithium hydroxide, mCPBA = meta-chloroperoxybenzoic acid, MgSO₄ = magnesium sulfate, min = minute(s), mL = milliliter, MPLC = medium pressure liquid chromatography, MS = mass spectrum, nBuLi = n-

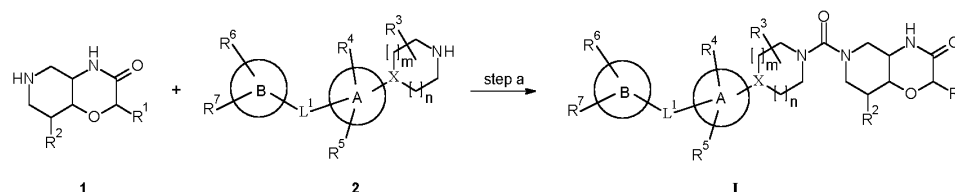
20 butyllithium, NaBH₃CN = sodium cyanoborohydride, NaH = sodium hydride, NaHCO₃ = sodium hydrogen carbonate, NaNO₂ = sodium nitrite, NaBH(OAc)₃ = sodium triacetoxyborohydride, NaOH = sodium hydroxide, Na₂CO₃ = sodium carbonate, Na₂SO₄ = sodium sulfate, Na₂S₂O₃ = sodium thiosulfate, NBS = N-bromosuccinimide, nBuLi = n-butyllithium, NEt₃ = triethylamine (TEA), NH₄Cl = ammonium chloride, NMP = N-

25 methyl-2-pyrrolidone, OAc = Acetoxy, T₃P = propylphosphonic anhydride, PE = petroleum ether, PG = protective group, Pd-C = palladium on activated carbon, PdCl₂(dppf)-CH₂Cl₂ = 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex, Pd₂(dba)₃ = tris(dibenzylideneacetone)dipalladium(0), Pd(OAc)₂ = palladium(II) acetate, Pd(OH)₂ = palladium hydroxide, Pd(PPh₃)₄ =

30 tetrakis(triphenylphosphine)palladium(0), PTSA = p-toluenesulfonic acid, R = any group, RT = room temperature, SFC = Supercritical Fluid Chromatography, S-PHOS = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, TBAI = tetra butyl ammonium iodine, TEA = triethylamine, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMEDA = N,N,N',N'-tetramethylethylenediamine, ZnCl₂ = zinc chloride, Hal = halogen.

- 29 -

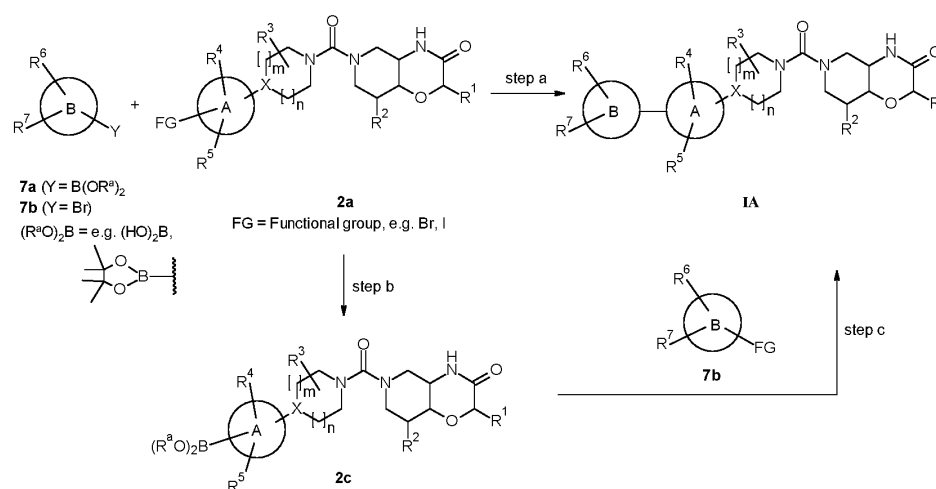
Compounds of formula **I** wherein A, B, L¹, X, m, n, R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ are as described herein can be synthesized in analogy to literature procedures and/or as depicted for example in [Scheme 1](#).



5 [Scheme 1](#)

Accordingly, 4a,5,6,7,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-ones **1** are reacted with intermediates **2** in the presence of a urea forming reagent such as bis(trichloromethyl) carbonate using a suitable base and solvent such as, e.g. sodium bicarbonate in DCM, to give compounds of formula **I** ([step a](#)). Further urea forming reagents include but are not limited to phosgene, trichloromethyl chloroformate, (4-nitrophenyl)carbonate or 1,1'-carbonyldiimidazole. Reactions of this type and the use of these reagents are widely described in literature (e.g. G. Sartori et al., *Green Chemistry* **2000**, 2, 140). A person skilled in the art will acknowledge that the order of the addition of the reagents can be important in this type of reactions due to the reactivity and stability of the intermediary formed carbamoyl chlorides, as well as for avoiding formation of undesired symmetrical urea by-products.

Compounds **IA** in which R¹ to R⁷, m, n, L¹ A and B are as described herein, can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in [Scheme 1a](#).



Scheme 1a

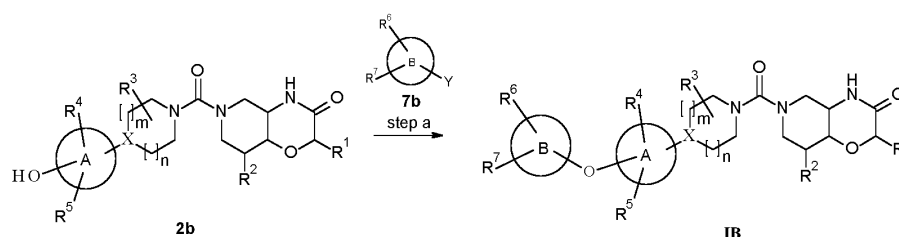
- Intermediates **2a**, prepared in analogy to scheme 1, can be reacted with aryl or heteroaryl boronic acids **7a** ($Y = B(OH)_2$) or boronic esters, $Y =$ e.g. 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (pinacol) ester), either commercially available or prepared using
- 5 literature procedures as described for example in “Boronic Acids - Preparation and Applications in Organic Synthesis and Medicine” by Dennis G. Hall (ed.) 1st Ed., 2005, John Wiley & Sons, New York) using a suitable catalyst (e.g. dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) dichloromethane adduct, tetrakis(triphenylphosphine)palladium(0) or palladium(II)acetate with triphenylphosphine)
- 10 in an appropriate solvent (e.g. dioxane, dimethoxyethane, water, toluene, DMF or mixtures thereof) and a suitable base (e.g. Na_2CO_3 , $NaHCO_3$, KF, K_2CO_3 or TEA) at temperatures between room temperature and the boiling point of the solvent or solvent mixture, to yield compounds **IA** (step a). Suzuki reactions of this type are broadly described in literature (e.g. A. Suzuki, Pure Appl. Chem. 1991, 63, 419-422; A. Suzuki, N. Miyauchi, Chem. Rev. 1995, 95, 2457-2483; A. Suzuki, J. Organomet. Chem. 1999, 576, 147-168; V. Polshettiwar et al., Chem. Sus. Chem. 2010, 3, 502-522) and are well known to those skilled in the art. Alternatively, aryl- or heteroaryl-trifluoroborates (**7a** with $Y = BF_3$) can be used in the cross-coupling reaction applying a palladium catalyst such as, e.g. tetrakis(triphenylphosphine)-palladium(0), palladium(II) acetate or dichloro[1,1'-
- 20 bis(diphenylphosphino)ferrocene]-palladium(II) dichloromethane adduct in the presence of a suitable base such as cesium carbonate or potassium phosphate in solvents such as toluene, THF, dioxane, water or mixtures thereof, at temperatures between room temperature and the boiling point of the solvent or solvent mixture (step a). Alternatively, the bromine or iodine in intermediates **2a** can be exchanged to a boronic
- 25 acid or boronic ester group using for examples the methods described under step a) to give intermediates **2c** (step b).
- Intermediates **2c** can then be reacted with intermediates **7b** in which FG is for example bromine, either commercially available to prepared in analogy to literature methods, applying the reaction conditions described before to furnish compounds **IA** (step c).
- 30 Furthermore, intermediates **7b** in which Y is preferably bromine can be subjected to a cross-electrophile coupling with intermediates **2a** with FG preferably being bromine, prepared in analogy to scheme 1, under irradiation with a 420 nm blue light lamp using an appropriate photo catalyst such as $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ ([4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-N1,N1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-

- 31 -

N]phenyl-C]Iridium(III) hexafluorophosphate), a Nickel catalyst like NiCl₂ glyme (dichloro(dimethoxyethane)nickel), 4,4'-di-tert-butyl-2,2'-dipyridyl and tris(trimethylsilyl)silane, in the presence of a suitable base such as anhydrous sodium carbonate in a solvent like DME. Reactions of this type are described in literature, e.g. *J.*

5 *Am. Chem. Soc.* **2016**, 138, 8084. (step a).

Compounds of formula **IB** wherein A, B, R¹ to R⁷, *m*, *n*, and X and are as described herein and L¹ is oxygen, may be synthesized according to the general procedure outlined in Scheme 1b.



10 Scheme 1b

Accordingly, intermediates **2b** (obtainable e.g. by the general procedure outlined in Scheme 3), can be transformed to compound **IB**, by applying nucleophilic aromatic substitution reaction. Treatment of hydroxy intermediates **2b** with a suitable heteroaryl compound **7b**, wherein Y is a suitable halogen such as fluorine, chlorine or bromine,

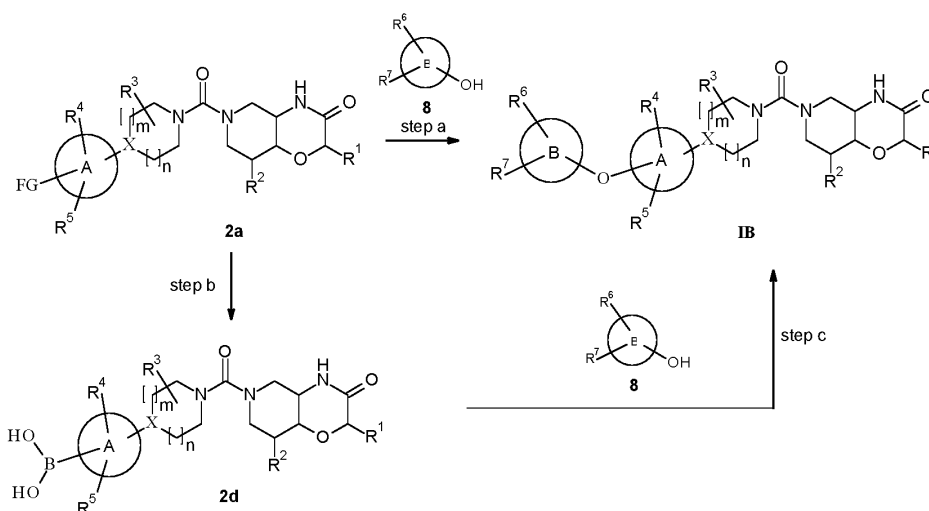
15 preferably fluorine or chlorine, wherein R⁶ and R⁷ are described herein, such as 2-chloro-pyrimidine, 2-chloro-4-methylpyrimidine, 3-chloropyridazine, 3,4-dichloropyridazine, 2-chloro-4-methoxypyrimidine, 2-chloro-4-trifluoromethylpyrimidine, 3-fluoro-4-methylpyridine, 3,5-difluoropyridine, 3-chloro-5-fluoro-pyridine, 3-fluoropyridine, 2-fluorobenzonitrile, 2-fluoro-6-methylpyridine, 4-bromo-2-chloro-pyrimidine, 2-chloro-4-cyclopropylpyrimidine, 4-chloro-3-fluoropyridine and 4-chloro-2-

20 (methylsulfonyl)pyrimidine using a suitable base such as K₂CO₃ or Cs₂CO₃ in an appropriate solvent such as DMSO, DMF or NMP at temperatures ranging from 0°C up to 200°C, optionally applying microwave heating, yield compounds of formula **IB** (step a).

Alternatively, compounds of formula **IB** wherein A, B, R¹ to R⁷, *m*, *n* and X and are as described herein and L¹ is oxygen, may be synthesized according to the general procedure outlined in Scheme 1c.

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- 32 -

**Scheme 1c**

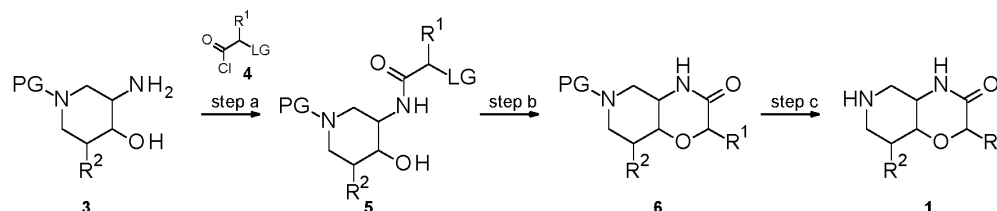
Accordingly, intermediates of type **2a** (obtainable e.g. by the general procedure outlined in Scheme 4), wherein FG is a suitable halogen such as chlorine or bromine, preferably

- 5 bromine, can be transformed to compound **IB**, by applying Buchwald-Hartwig cross-coupling reaction. Treatment of intermediates **2a** with a suitable phenol compound **8**, wherein R^6 and R^7 are described herein, such as phenol, using a suitable catalyst system such as $Pd(OAc)_2$ and 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl in the presence of a base such as K_3PO_4 in an appropriate solvent such as toluene at temperatures
- 10 ranging from room temperature up to the boiling point of the solvent, optionally applying microwave heating, yield compounds of formula **IB** (step a).

Alternatively, the bromine in intermediates **2a** can be exchanged to a boronic acid group to give intermediates **2d** (obtainable e.g. by the general procedure outlined in Scheme 4) (step b).

- 15 Intermediates **2d** can be then transformed to compound **IB**, by applying Chan-Lam cross coupling reaction. Treatment of boronic acid intermediates **2d** with a suitable phenol compound **8**, wherein R^6 and R^7 are described herein, such as 2-fluorophenol, 3-fluorophenol, 4-fluorophenol, 2,4-difluorophenol, 2-chlorophenol, 3-chlorophenol, 4-chlorophenol, 2-methylphenol and 3-trifluoromethylphenol, in presence of TEA,
- 20 $Cu(OAc)_2$ and molecular sieves in a solvent like DCM, DCE or CH_3CN at room temperature, yields compounds of formula **IB** (step c).

Intermediates **1** may be synthesized as depicted for example in Scheme 2 and/or in analogy to methods described in literature.



Scheme 2

- Thus, 3-aminopiperidin-4-ol derivatives **3** in which “PG” signifies a suitable protective group such as a Cbz or Boc protective group can be acylated for example with acyl chlorides **4** in which R¹ is as defined herein and “LG” signifies a suitable leaving group (e.g., Cl or Br), using a suitable base such as sodium or potassium carbonate, sodium hydroxide or sodium acetate in an appropriate solvent such as THF, water, acetone or mixtures thereof, to provide intermediates **5** (step a). Intermediates **4** are either commercially available or can be prepared according to literature methods in achiral (R¹ = H) racemic (R¹ not H) or enantiomerically pure form (R¹ not H).

Intermediates **5** can be cyclized to intermediates **6** using methods well known in the art, for example by treatment of **5** with sodium hydride in THF or potassium tert-butoxide in IPA and water (step b). Reactions of that type are described in literature (e.g. Z. Rafinski et al., *J. Org. Chem.* **2015**, 80, 7468; S. Dugar et al., *Synthesis* **2015**, 47(5), 712; WO2005/066187).

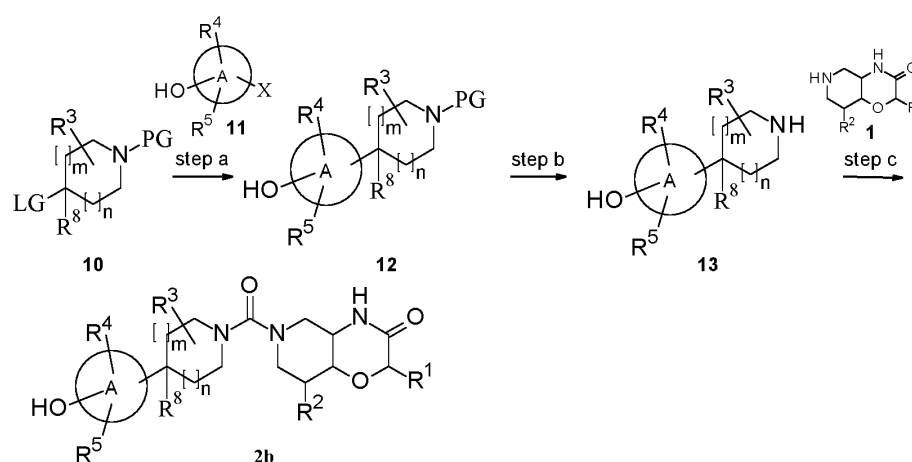
Removal of the protective group in intermediates **6**, applying methods known in the art (e.g., a Boc group using TFA in DCM at temperatures between 0°C and room temperature, a Cbz group using hydrogen in the presence of a suitable catalyst such as Pd or Pd(OH)₂ on charcoal in a suitable solvent such as MeOH, EtOH, EtOAc or mixtures thereof and as described for example in “Protective Groups in Organic Chemistry” by T.W. Greene and P.G.M. Wuts, 4th Ed., 2006, Wiley N.Y.), furnishes intermediates **1** (step c).

Intermediates **1** can be obtained as mixtures of diastereomers and enantiomers, respectively, or as single stereoisomers depending on whether racemic mixtures or enantiomerically pure forms of cis- or trans-3-aminopiperidin-4-ol derivatives **3** are employed in their syntheses. Intermediates **3** are commercially available and their synthesis has also been described in literature (e.g. WO2005/066187; WO2011/0059118; WO2016/185279). Optically pure cis-configured intermediates **1B** and **1C** can be obtained for example according to Scheme 3 by chiral separation of commercially available rac-

- 34 -

(4aR,8aS)-4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one (**1A**) (optionally in form of a salt such as, e.g. a hydrochloride salt) using methods known in the art, e.g. by diastereomeric salt crystallization or by chiral chromatography (step a).

- 5 In some embodiments, intermediates **2** are intermediates of type **2b**. Intermediates **2b** in which A is aryl, $m = n = 0$, R^1 , R^2 , R^3 , R^4 , R^5 and R^8 are as described herein, can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in Scheme 3.



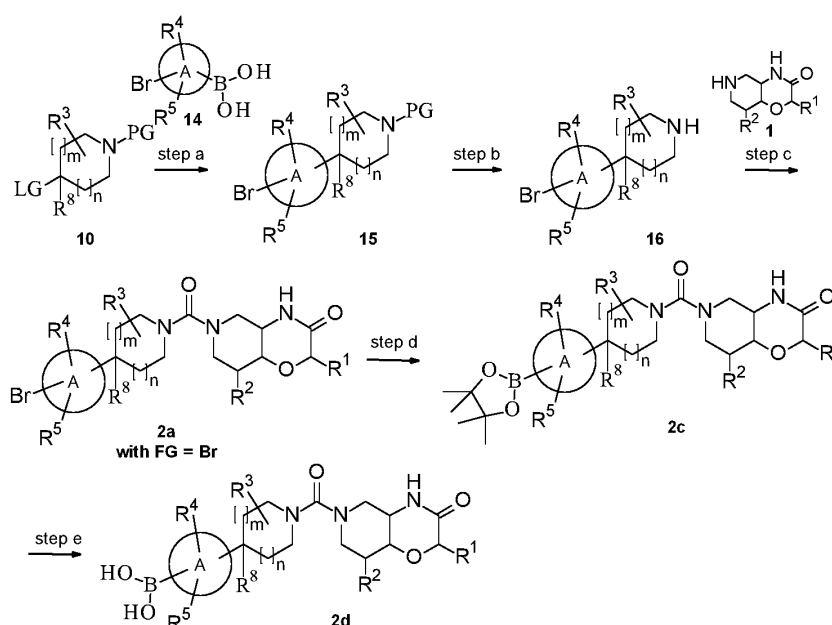
10 Scheme 3

- Protected amines **10**, either commercially available or prepared by methods known in the art, wherein LG is a suitable leaving group such as bromine or iodine, preferably bromine, m , n and R^3 are as described herein and PG is a suitable protecting group such as, e.g. a Boc, Cbz or Bn, can be subjected to a cross-electrophile coupling with aryl bromides **11**, wherein X is bromine, R^4 and R^5 are as described herein, such as 4-bromophenol under irradiation with a 420 nm blue light lamp using an appropriate photo catalyst such as [Ir{dF(CF₃)ppy}2(dtbbpy)]PF₆ ([4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-N1,N1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-N]phenyl-C]Iridium(III) hexafluorophosphate), a Nickel catalyst like NiCl₂ glyme (dichloro(dimethoxyethane)nickel), 4,4'-di-tert-butyl-2,2'-dipyridyl and tris(trimethylsilyl)silane, in the presence of a suitable base such as anhydrous sodium carbonate in a solvent like DME. Reactions of this type are described in literature, e.g. *J. Am. Chem. Soc.* **2016**, 138, 8084. (step a). Removal of the protective group from intermediates **12** applying methods well known in the art and as described under Scheme

- 35 -

2, step c, furnishes intermediates **13** (step b). Amines **13** can be then coupled with intermediates **1** applying for example the conditions outlined under Scheme 1, step a, to give intermediates **2b** (step c).

- 5 In some embodiments, intermediates **2** are intermediates of type **2a**, **2c** or **2d**. Intermediates **2a**, **2c** and **2d** in which A is aryl, $m = n = 0$, R^1 , R^2 , R^3 , R^4 , R^5 and R^8 are as described herein, can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in Scheme 4.



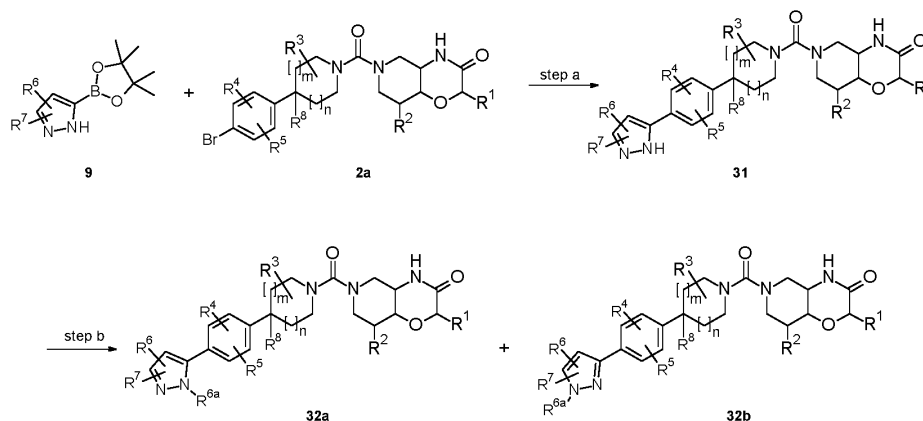
10 Scheme 4

- Protected amines **10**, either commercially available or prepared by methods known in the art, wherein LG is a suitable leaving group such as such bromine or iodine, preferably iodine, m , n and R^3 are as described herein and PG is a suitable protecting group such as, e.g. a Boc, Cbz or Bn, can be subjected to Suzuki-Miyaura cross coupling reaction with
- 15 arylboronic acids **14**, such as 4-bromophenylboronic acid, using a suitable Nickel catalyst such as nickel(II) iodide in the presence of rac-(1R,2R)-2-aminocyclohexan-1-ol and a suitable base such as sodium bis(trimethylsilyl)amide in an appropriate solvent like iPrOH, dioxane, THF or DME, preferably iPrOH at temperatures between room temperature and the boiling point of the solvent, optionally applying microwave heating, to yield
- 20 intermediates **15**. Reactions of this type are described in literature, e.g. *ChemistrySelect*. **2017**, 2, 8841 (step a). Removal of the protective group from intermediates **15** applying

- 36 -

methods well known in the art and as described under Scheme 2, step c, furnishes intermediates **16** (step b). Amines **16** can be then coupled with intermediates **1** applying for example the conditions outlined under Scheme 1, step a, to give intermediates **2a**, in which FG is bromine (step c). The bromo substituent in intermediates **2a** can be converted into a boronic acid or boronic ester (e.g. pinacol ester) according to literature procedures as described for example in “Boronic Acids - Preparation and Applications in Organic Synthesis and Medicine” by Dennis G. Hall (ed.) 1st Ed., 2005, John Wiley & Sons, New York) using a suitable catalyst such as PdCl₂(dppf).CH₂Cl₂ in the presence of bis(pinacolato)diboron and a suitable base such as Na₂CO₃, NaHCO₃, KF, KOAc or TEA in an appropriate solvent like dioxane, THF, DME, water or DMF, or mixtures thereof, preferably dioxane at temperatures between room temperature and the boiling point of the solvent, or mixtures thereof, optionally applying microwave heating, to yield intermediates **2c** (step d). Finally, hydrolysis of the pinacolyl ester in intermediates **2c** can be achieved by methods known in literature (e.g. *Tetrahedron letters* **2005**, 46, 7899) or using NaIO₄ in presence of NH₄OAc in a mixture of water and acetone at around room temperature to give intermediates **2d** (step e).

Compounds **31**, **32a** and **32b** in which R¹ to R⁷, R⁸, m and n are as described herein, R^{6a} is C₁₋₆-alkyl, L¹ is a covalent bond, A is phenyl and B is a 1-(C₁₋₆-alkyl)-substituted pyrazole 3-yl or pyrazole 5-yl, can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in Scheme 5.



Scheme 5

Commercially available boronic acid ester intermediates **9** can be subjected to a Suzuki coupling reaction with intermediates **2a**, prepared for example according to scheme 3,

- 37 -

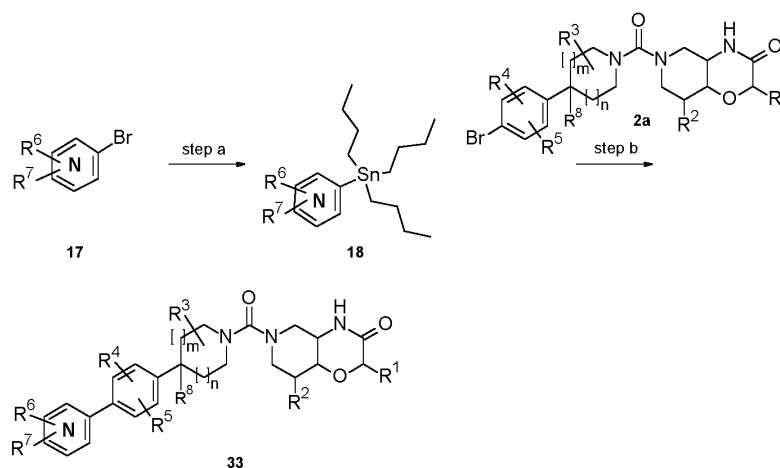
applying the reaction conditions as described under scheme 1a, step a, to provide compounds **31** (step a).

Compounds **31** can be alkylated with an alkylating agent of type $R^{6a}LG$ in which LG is a suitable leaving group such as chlorine, bromine, iodine, OSO_2 alkyl (e.g. mesylate

- 5 (methanesulfonate), OSO_2 fluoroalkyl (e.g. triflate (trifluoromethanesulfonate) or OSO_2 aryl (e.g. tosylate (p-toluenesulfonate)), using a suitable base in an appropriate solvent (e.g. sodium hydride in DMF or cesium carbonate in DMF) at temperatures between 0 °C and the boiling temperature of the solvent to provide the regioisomeric compounds **32a** and **32b** that can be separated for example by column chromatography (step b).

10

Compounds **33** in which R^1 to R^8 , m and n are as described herein, L^1 is a covalent bond, A is phenyl and B is an optionally further substituted pyridine, can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in Scheme 6.



15

Scheme 6

The bromine in commercially available 2-bromo-3-chloro-pyridine **17** can be converted into a tri-*n*-butyltin group by methods known in the art, for example by first carrying out a bromo lithium exchange reaction with *n*-BuLi in a suitable solvent such as toluene in a

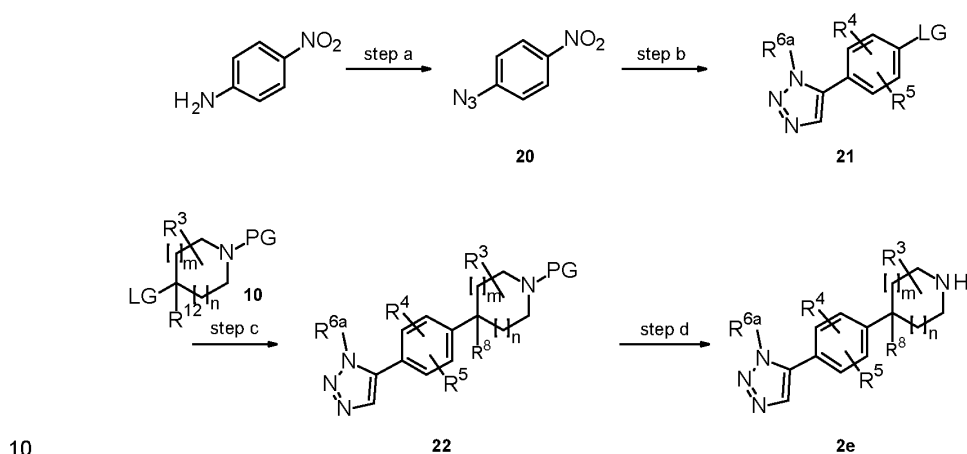
20 temperature range from, e.g. -78°C to RT and reacting the intermediate lithium species with tri-*N*-butyltin chloride to provide intermediates **18** (step a).

Intermediates **18** can be reacted with intermediates **2a** using a suitable catalyst and solvent such as, e.g. tetrakis(triphenylphosphine)-palladium(0) in DMF at temperatures between room temperature and the boiling point of the solvent or solvent mixture to provide

- 38 -

compounds **33** (step a). Stille reactions of that type are well known in the art and described in literature, e.g. *Org. React.* **1997**, 50, 1-652, *ACS Catal.* 2015, 5, 3040–3053.

In some embodiments, intermediates **2** are intermediates of type **2e**. Intermediates of type **2e** in which R^3 , R^4 , R^5 , R^8 , m and n are defined as herein, R^{6a} is C_{1-6} -alkyl, L^1 is a covalent bond, A is phenyl and B is a 1-alkyl-substituted triazole 5-yl can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in Scheme 7.



Scheme 7

Commercially available 4-nitroaniline can be converted into intermediate **20** by methods known in the art, for example using tert-butyl nitrite and trimethylsilylazide in an appropriate solvent such as ACN (step a).

Reaction of intermediates **20** with an acetophenone (e.g., 4'-bromoacetophenone) and amines of type R^{6b} - NH_2 in a suitable acid and solvent system such as AcOH in toluene, optionally using molecular sieves preferably at elevated temperatures furnishes triazole intermediates **21**, wherein LG is a suitable leaving group, e.g. a halogen, in particular bromo (step b). Reactions of this type have been described in literature, e.g. Chem.

Commun., 2016, 52, 2885.

Intermediates **21** can be subjected to a cross-electrophile coupling reaction with commercially available intermediate **10**, wherein LG is a suitable leaving group such as bromo or iodo, preferably bromo, m , n and R^3 are as described herein and PG is a suitable

- 39 -

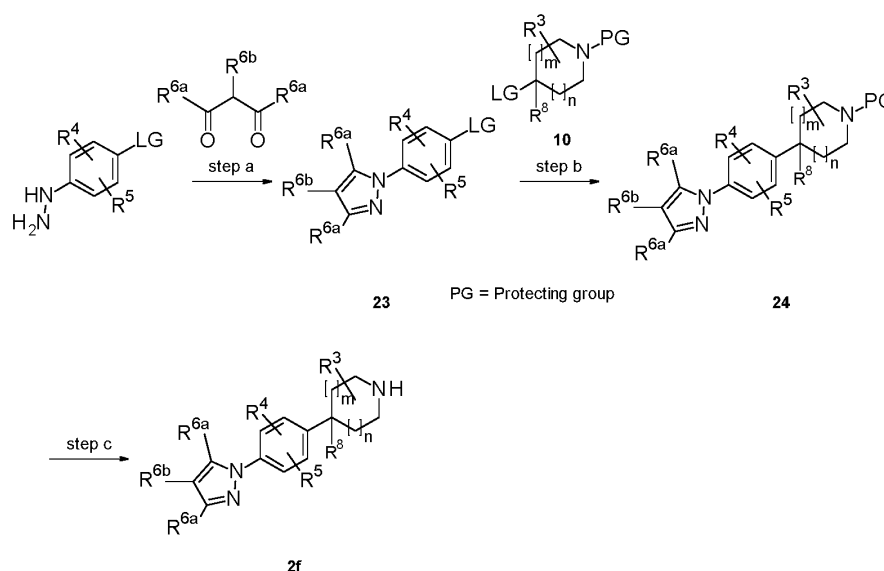
protecting group, such as Boc, applying for example the reaction conditions described under scheme 1a, step a, to provide intermediates **22** (step c).

Removal of the protecting group using for example TFA in DCM at temperatures between 0°C and room temperature, yields intermediates **2e** (step d).

5

In some embodiments, intermediates **2** are intermediates of type **2f**. Intermediates of type **2f** in which R^3 , R^4 , R^5 , R^8 , m and n are as defined herein, R^{6a} is C_{1-6} -alkyl or halo- C_{1-6} -alkyl, R^{6b} is hydrogen, C_{1-6} -alkyl or halo- C_{1-6} -alkyl, L^1 is a covalent bond, A is phenyl and B is pyrazole-1-yl can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in Scheme 8.

10



Scheme 8

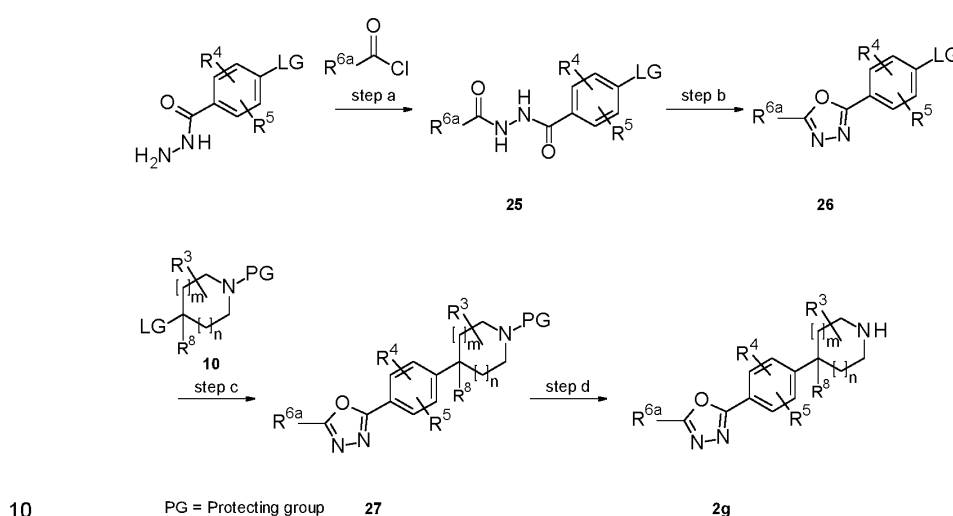
Intermediates **23** can be prepared for example by cyclocondensation of 1,3-dicarbonyl compounds with commercially available and optionally substituted hydrazines (e.g., (4-bromophenyl)hydrazines) in the presence of copper(II) nitrate trihydrate in a suitable solvent such as ACN (step a).

Intermediates **23** can be subjected to a cross-electrophile coupling reaction with intermediates of type **10** in which PG signifies a suitable protecting group such as Cbz or Boc, and LG refers to a suitable leaving group, such as a halogen, in particular bromo, applying for example the reaction conditions described under scheme 1a, step a, to provide intermediates **24** (step b).

- 40 -

Removal of the protective group applying published procedures and as described under scheme 7, step d, furnishes intermediates **2f** (step c).

In some embodiments, intermediates **2** are intermediates of type **2g**. Intermediates of type **2g** in which R^3 , R^4 , R^5 , R^8 , m and n are as defined herein, R^{6a} is C_{1-6} -alkyl, L^1 is a covalent bond, A is phenyl and B is a 5-substituted-1,3,4-oxadiazol-2-yl can be prepared by methods known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in Scheme 9.



Scheme 9

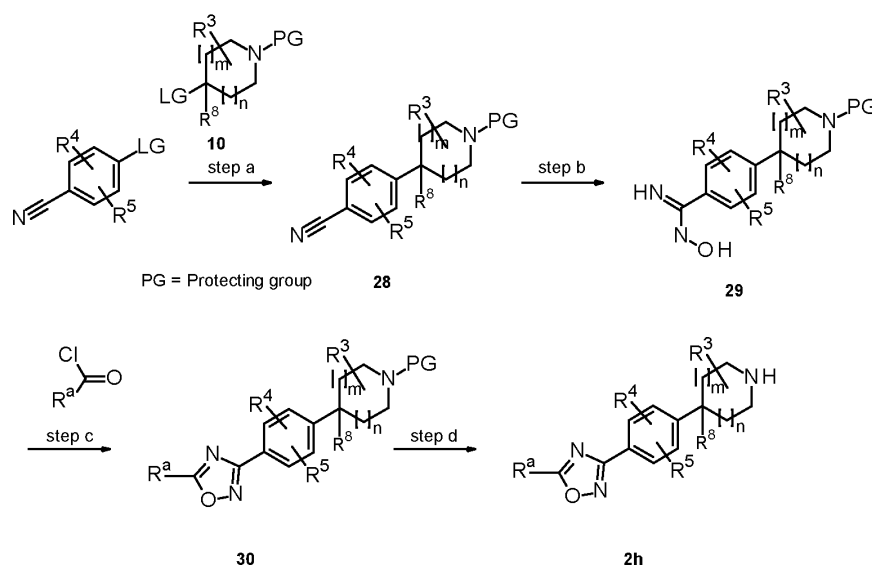
Commercially available hydrazides (e.g., 4-bromobenzoic hydrazide) and acid chlorides $R^{6a}C(O)Cl$ can be reacted in the presence of a suitable base in an appropriate solvent such as DIPEA in DCM to yield intermediate **25** (step a).

Intermediates **25**, in which LG refers to a suitable leaving group, such as halogen, in particular bromo, can be dehydrated for example using pTsOH in toluene preferably at elevated temperatures up to the boiling point of the solvent to provide intermediates **26** (step b).

Intermediates **26** can be subjected for example to a cross-electrophile coupling reaction with intermediates of type **10** applying for example the reaction conditions described under scheme 1a, step a, to provide intermediates **27** (step c).

Removal of the protective group applying published procedures and as described under scheme 7, step d furnishes intermediates **2g** (step d).

In some embodiments, intermediates **2** are intermediates of type **2h**. Intermediates of type **2h** in which in which R³, R⁴, R⁵, R⁸, m and n are as defined herein, R^{6a} is C₁₋₆-alkyl, L¹ is a covalent bond, A is phenyl and B is a 5-substituted-1,2,4-oxadiazol-3-yl can be prepared
5 by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in Scheme 10.



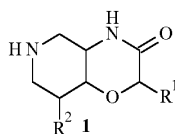
Scheme 10

Commercially available or prepared by methods known in the art optionally substituted benzonitriles (e.g., 4-bromobenzonitriles) can be subjected to a cross-electrophile coupling reaction with intermediates of type **10** applying for example the reaction conditions described under scheme 1a, step a, to provide intermediates **28** (step a). Reaction of intermediates **28** with hydroxylamine hydrochloride in a suitable solvent or solvent mixture and using an appropriate base such as Na₂CO₃ in EtOH and water, preferably at elevated temperatures, gives the phenylamidoxime intermediates **29** (step b). Intermediates **29** can then be reacted with acid chlorides R^{6a}C(O)Cl in the presence of a suitable base and solvent such as DIPEA in toluene at temperatures ranging from RT to the boiling point of the solvent or solvent mixture to provide intermediates **30** (step c). Removal of the protective group applying published procedures and as described under scheme 7, step d, furnishes intermediates **2h** (step d).

- 42 -

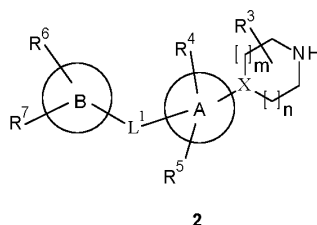
In one aspect, the present invention provides a process of manufacturing the compounds of formula (I) as described herein, comprising:

reacting 4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-ones **1**, wherein R^1 and R^2 are as defined herein,



5

with a heterocyclic amine **2**, wherein A, B, L^1 , X, m, n, and R^3 to R^7 are as defined herein

**2**

10 in the presence of a base and a urea forming reagent,
to form said compounds of formula (I).

In one embodiment, there is provided a process according to the invention, wherein said base is sodium bicarbonate.

In one embodiment, there is provided a process according to the invention, wherein said urea forming reagent is selected from bis(trichloromethyl) carbonate, phosgene,
15 trichloromethyl chloroformate, (4-nitrophenyl)carbonate and 1,1'-carbonyldiimidazole,
preferably wherein said urea forming reagent is bis(trichloromethyl) carbonate.

In one aspect, the present invention provides a compound of formula (I) as described herein, when manufactured according to any one of the processes described herein.

MAGL Inhibitory Activity

20 Compounds of the present invention are MAGL inhibitors. Thus, in one aspect, the present invention provides the use of compounds of formula (I) as described herein for inhibiting MAGL in a mammal.

In a further aspect, the present invention provides compounds of formula (I) as described herein for use in a method of inhibiting MAGL in a mammal.

- 43 -

In a further aspect, the present invention provides the use of compounds of formula (I) as described herein for the preparation of a medicament for inhibiting MAGL in a mammal.

In a further aspect, the present invention provides a method for inhibiting MAGL in a mammal, which method comprises administering an effective amount of a compound of
5 formula (I) as described herein to the mammal.

Compounds of formula (I) were profiled for MAGL inhibitory activity by determining the enzymatic activity by following the hydrolysis of the natural substrate 2-arachidonoylglycerol (2-AG) resulting in arachidonic acid, which can be followed by mass spectrometry. This assay is hereinafter abbreviated “2-AG assay”.

10 The 2-AG assay was carried out in 384 well assay plates (PP, Greiner Cat# 784201) in a total volume of 20 μ L. Compound dilutions were made in 100% DMSO (VWR Chemicals 23500.297) in a polypropylene plate in 3-fold dilution steps to give a final concentration range in the assay from 12.5 μ M to 0.8 pM. 0.25 μ L compound dilutions (100% DMSO) were added to 9 μ L MAGL in assay buffer (50 mM TRIS (GIBCO, 15567-027), 1 mM
15 EDTA (Fluka, 03690-100 mL), 0.01% (v/v) Tween. After shaking, the plate was incubated for 15 min at RT. To start the reaction, 10 μ L 2-arachidonoylglycerol in assay buffer was added. The final concentrations in the assay was 50 pM MAGL and 8 μ M 2-arachidonoylglycerol. After shaking and 30 min incubation at RT, the reaction was quenched by the addition of 40 μ L of ACN containing 4 μ M of d8-arachidonic acid. The
20 amount of arachidonic acid was traced by an online SPE system (Agilent Rapidfire) coupled to a triple quadrupole mass spectrometer (Agilent 6460). A C18 SPE cartridge (G9205A) was used in an ACN/water liquid setup. The mass spectrometer was operated in negative electrospray mode following the mass transitions 303.1 $\rightarrow$ 259.1 for arachidonic acid and 311.1 $\rightarrow$ 267.0 for d8-arachidonic acid. The activity of the compounds was
25 calculated based on the ratio of intensities [arachidonic acid / d8-arachidonic acid].

Table 1

Example	IC ₅₀ MAGL [nM]
1	0.2
2	0.02

Example	IC ₅₀ MAGL [nM]
3	75.4
4	2.5

- 44 -

Example	IC₅₀ MAGL [nM]
5	23.8
6	132.8
7	0.5
8	4.3
9	0.9
10	2.3
11	42.9
12	23.5
13	12.7
14	13.4
15	0.11
16	0.05
17	0.10
18	0.05
19	0.01
20	0.06
21	0.03
22	0.06
23	0.2
24	0.04
25	4.2

Example	IC₅₀ MAGL [nM]
26	3.9
27	0.3
28	6.3
29	90.9
30	0.7
31	91.9
32a	0.2
32b	6.5
33	2.7
34	22.9
35	17.4
36	0.9
37	2.4
38	8.5
39	6.7
40	73.1
41	24.6
42	153.2
43	19.3
44	67.7
45	133.7

- 45 -

Example	IC ₅₀ MAGL [nM]
46	17.5
47	1.4
48	31.5
49	2.4
50	4.3
51	123.8
52	1.3

Example	IC ₅₀ MAGL [nM]
53	12.9
54	10.4
55	10.3
56	15.5
57	17.8
58	1096.3

In one aspect, the present invention provides compounds of formula (I) and their pharmaceutically acceptable salts or esters as described herein, wherein said compounds of formula (I) and their pharmaceutically acceptable salts or esters have IC₅₀'s for MAGL inhibition below 25 μM, preferably below 10 μM, more preferably below 5 μM as measured in the MAGL assay described herein.

In one embodiment, compounds of formula (I) and their pharmaceutically acceptable salts or esters as described herein have IC₅₀ (MAGL inhibition) values between 0.000001 μM and 25 μM, particular compounds have IC₅₀ values between 0.000005 μM and 10 μM, further particular compounds have IC₅₀ values between 0.00005 μM and 5 μM, as measured in the MAGL assay described herein.

Using the Compounds of the Invention

In one aspect, the present invention provides compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for use as therapeutically active substance.

In a further aspect, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.

- 46 -

In one embodiment, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the treatment or prophylaxis of neuroinflammation and/or neurodegenerative diseases in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I), or
5 pharmaceutically acceptable salts thereof, as described herein for the treatment or prophylaxis of neurodegenerative diseases in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the treatment or prophylaxis of cancer in a mammal.

10 In one embodiment, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the treatment or prophylaxis of inflammatory bowel disease in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the treatment or
15 prophylaxis of pain in a mammal.

In one aspect, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine,
20 depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain, spasticity associated with pain, abdominal pain, abdominal pain associated with irritable bowel syndrome and/or visceral pain in a mammal.

In a preferred embodiment, the present invention provides the use of compounds of
25 formula (I), or pharmaceutically acceptable salts thereof, as described herein for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease and/or Parkinson's disease in a mammal.

In a particularly preferred embodiment, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described
30 herein for the treatment or prophylaxis of multiple sclerosis in a mammal.

- 47 -

In one aspect, the present invention provides compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.

- 5 In one embodiment, the present invention provides compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for use in the treatment or prophylaxis of neuroinflammation and/or neurodegenerative diseases in a mammal.

In one embodiment, the present invention provides compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for use in the treatment or
10 prophylaxis of cancer in a mammal.

In one embodiment, the present invention provides compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for use in the treatment or prophylaxis of neurodegenerative diseases in a mammal.

- In one embodiment, the present invention provides compounds of formula (I), or
15 pharmaceutically acceptable salts thereof, as described herein for use in the treatment or prophylaxis of inflammatory bowel disease in a mammal.

In one embodiment, the present invention provides compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for use in the treatment or prophylaxis of pain in a mammal.

- 20 In one aspect, the present invention provides compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for use in the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic
25 pain, chemotherapy induced neuropathy, acute pain, chronic pain, spasticity associated with pain, abdominal pain, abdominal pain associated with irritable bowel syndrome and/or visceral pain in a mammal.

In a preferred embodiment, the present invention provides compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for use in the treatment or

- 48 -

prophylaxis of multiple sclerosis, Alzheimer's disease and/or Parkinson's disease in a mammal.

In a particularly preferred embodiment, the present invention provides compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for use in the
5 treatment or prophylaxis of multiple sclerosis in a mammal.

In one aspect, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the preparation of a medicament for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.

10 In one embodiment, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the preparation of a medicament for the treatment or prophylaxis of neuroinflammation and/or neurodegenerative diseases in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I), or
15 pharmaceutically acceptable salts thereof, as described herein for the preparation of a medicament for the treatment or prophylaxis of neurodegenerative diseases in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the preparation of a medicament for the treatment or prophylaxis of cancer in a mammal.

20 In one embodiment, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the preparation of a medicament for the treatment or prophylaxis of inflammatory bowel disease in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the preparation of a
25 medicament for the treatment or prophylaxis of pain in a mammal.

In a further aspect, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described herein for the preparation of a medicament for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity,
30 stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon

- 49 -

carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain, spasticity associated with pain, abdominal pain, abdominal pain associated with irritable bowel syndrome and/or visceral pain in a mammal.

In a preferred embodiment, the present invention provides the use of compounds of
5 formula (I), or pharmaceutically acceptable salts thereof, as described herein for the preparation of a medicament for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease and/or Parkinson's disease in a mammal.

In a particularly preferred embodiment, the present invention provides the use of compounds of formula (I), or pharmaceutically acceptable salts thereof, as described
10 herein for the preparation of a medicament for the treatment or prophylaxis of multiple sclerosis in a mammal.

In one aspect, the present invention provides a method for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal, which method comprises administering an
15 effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as described herein to the mammal.

In one embodiment, the present invention provides a method for the treatment or prophylaxis of neuroinflammation and/or neurodegenerative diseases in a mammal, which method comprises administering an effective amount of a compound of formula (I), or a
20 pharmaceutically acceptable salt thereof, as described herein to the mammal.

In one embodiment, the present invention provides a method for the treatment or prophylaxis of neurodegenerative diseases in a mammal, which method comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as described herein to the mammal.

25 In one embodiment, the present invention provides a method for the treatment or prophylaxis of cancer in a mammal, which method comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as described herein to the mammal.

In one embodiment, the present invention provides a method for the treatment or
30 prophylaxis of inflammatory bowel disease in a mammal, which method comprises

- 50 -

administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as described herein to the mammal.

In one embodiment, the present invention provides a method for the treatment or prophylaxis of pain in a mammal, which method comprises administering an effective
5 amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as described herein to the mammal.

In a further aspect, the present invention provides a method for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine,
10 depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain, spasticity associated with pain, abdominal pain, abdominal pain associated with irritable bowel syndrome and/or visceral pain in a mammal, which method comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as
15 described herein to the mammal.

In a preferred embodiment, the present invention provides a method for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease and/or Parkinson's disease in a mammal, which method comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as described herein to the
20 mammal.

In a particularly preferred embodiment, the present invention provides a method for the treatment or prophylaxis of multiple sclerosis in a mammal, which method comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as described herein to the mammal.

25 Pharmaceutical Compositions and Administration

In one aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) as described herein and a therapeutically inert carrier.

In one embodiment, there is provided a pharmaceutical composition according to Example 47 or 48.

- 51 -

The compounds of formula (I) and their pharmaceutically acceptable salts and esters can be used as medicaments (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parentally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula (I) and their pharmaceutically acceptable salts and esters can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées and hard gelatin capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées and hard gelatin capsules.

Suitable adjuvants for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary in wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 20 mg per kg body weight, preferably about 0.5 mg to 4 mg per kg body weight (e.g. about 300 mg per person), divided into preferably 1-3 individual doses, which can consist, for example, of the same amounts, should be appropriate. It will,

however, be clear that the upper limit given herein can be exceeded when this is shown to be indicated.

Examples

The invention will be more fully understood by reference to the following examples. The claims should not, however, be construed as limited to the scope of the examples.

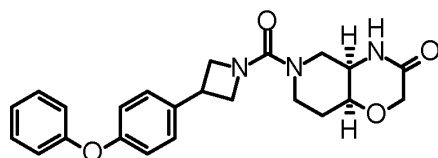
In case the preparative examples are obtained as a mixture of enantiomers, the pure enantiomers can be separated by methods described herein or by methods known to the man skilled in the art, such as e.g., chiral chromatography (e.g., chiral SFC) or crystallization.

All reaction examples and intermediates were prepared under an argon atmosphere if not specified otherwise.

Method A1

Example 1

(4aR,8aS)-6-(3-(4-Phenoxyphenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one

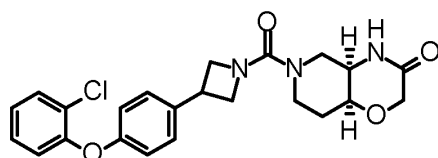


In a sealed tube, (4aR,8aS)-6-[3-(4-bromophenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (BB4 step c, 0.04 g, 0.110 mmol), phenol (0.014, 0.152 mmol), Pd(OAc)₂ (0.004 g, 0.016 mmol), 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (0.01 g, 0.024 mmol) and K₃PO₄ (0.043 g, 0.203 mmol) were mixed in toluene (0.68 mL). The reaction mixture was heated to 100°C over night. The mixture was diluted with EtOAc, poured into water and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated. The residue was purified by preparative HPLC to give the title compound (0.008, 17%) as an off white foam. MS (ESI): m/z =408.2 [M+H]⁺.

Method A2

Example 2

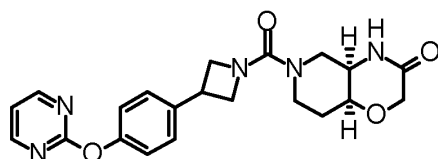
(4aR,8aS)-6-[3-[4-(2-Chlorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



- 5 To a solution of 4-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]phenyl]boronic acid (BB4, 0.025 g, 0.07 mmol), 2-chlorophenol (0.027 g, 0.21 mmol) and TEA (0.043 mL, 0.42 mmol) in MeCN (2 mL) was added 4A molecular sieves (0.03 g) and cupric acetate anhydrous (0.038 g, 0.21 mmol). The reaction mixture was stirred at 30°C under O₂ atmosphere for 16 hours. The mixture was quenched
- 10 with NH₄OH (0.3 mL) and H₂O (2 mL), and extracted with EtOAc (3 x 2 mL). The combined organic layers were evaporated to dryness and the residue was purified by preparative HPLC to yield the title product (0.007 g, 23%) as off-white solid. MS (ESI): m/z = 442.1 [M+H]⁺.

Method A3**Example 3**

(4aR,8aS)-6-[3-(4-Pyrimidin-2-yloxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



- In a sealed tube, (4aR,8aS)-6-[3-(4-hydroxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (BB3, 0.05 g, 0.150 mmol), 2-chloro-pyrimidine (0.026 g, 0.230 mmol, CAS RN 1722-12-9) and potassium carbonate (0.062 g, 0.450 mmol, CAS RN 584-08-7) were mixed in DMSO (2.5 mL). The reaction mixture was then heated to 80 °C for 12 hours. The mixture was diluted with EtOAc, poured into water and
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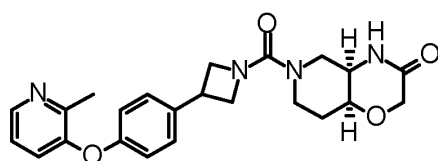
- 54 -

the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated. The residue was purified by preparative HPLC to yield the title product (0.039 g, 63%) as white solid. MS (ESI): m/z = 410.4 [M+H]⁺.

Method A4

5 Example 4

(4aR, 8aS)-6-[3-[4-[(2-Methyl-3-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

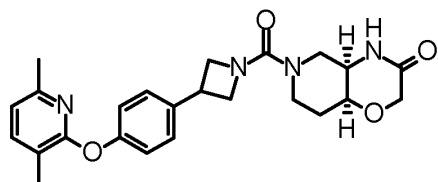


In a sealed tube, (4aR,8aS)-6-[3-(4-hydroxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-
10 hexahydropyrido[4,3-b][1,4]oxazin-3-one (BB3, 0.050 g, 0.150 mmol), 3-fluoro-2-methyl-
pyridine (0.046 g, 0.410 mmol) and Cs₂CO₃ (0.197 g, 0.6 mmol) were mixed in NMP (2
mL). The reaction mixture was then heated under microwave irradiation at 200°C for 1
hour. The mixture was diluted with EtOAc, poured into water and the aqueous layer was
extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄,
15 filtered and evaporated. The residue was purified by preparative HPLC to give the desired
product (0.007 g, 11%) as white solid. MS (ESI): m/z = 423.1 [M+H]⁺.

Method B1

Example 30

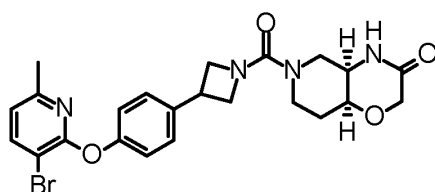
(4aR,8aS)-6-[3-[4-[(3,6-Dimethyl-2-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



- 55 -

To a solution of methylboronic acid (0.014 g, 0.24 mmol), K₂CO₃ (0.066 g, 0.48 mmol) and (4aR,8aS)-6-[3-[4-[(3-bromo-6-methyl-2-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (0.06 g, 0.12 mmol) in dioxane (2 mL) and water (0.5 mL) was added Pd(dppf)Cl₂ (0.008 g, 0.01 mmol) and the reaction mixture was heated to 100 °C for 12 hours. The mixture was filtered, the filtrate diluted with water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by preparative HPLC to give title product (0.009 g, 16%) as off-white solid. MS (ESI): m/z = 437.2 [M+H]⁺.

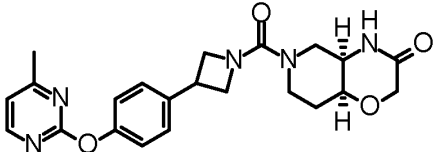
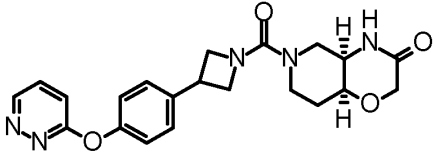
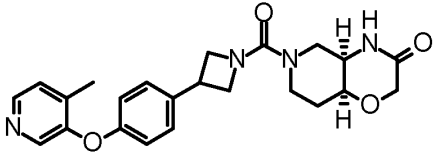
- 10 Step a) (4aR,8aS)-6-[3-[4-[(3-Bromo-6-methyl-2-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

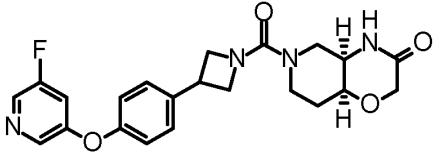
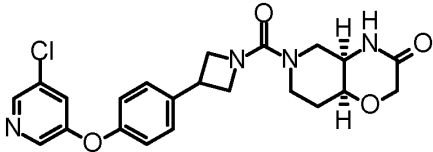
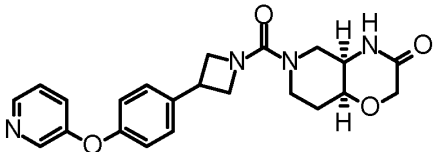


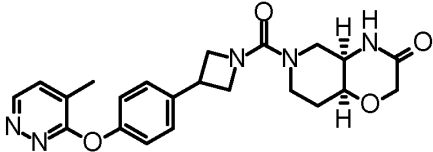
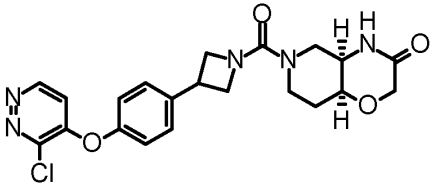
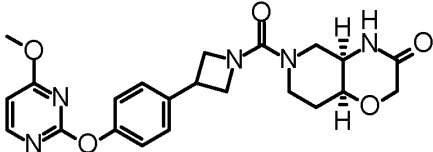
To a solution of (4aR,8aS)-6-[3-(4-hydroxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (BB3, 0.1 g, 0.3 mmol), Cs₂CO₃ (0.394 g, 1.21 mmol) in DMSO (5 mL) was added 3-bromo-2-fluoro-6-methyl-pyridine (0.086 g, 0.45 mmol) and the reaction mixture was heated to 50°C for 12 hours. The mixture was filtered and the filtrate purified by preparative HPLC to give the title product (0.08 g, 53%) as colorless foam. MS (ESI): m/z = 503.2 [M+2+H]⁺.

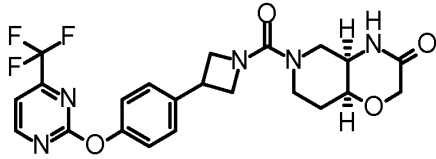
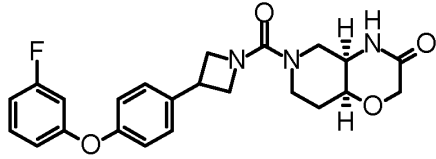
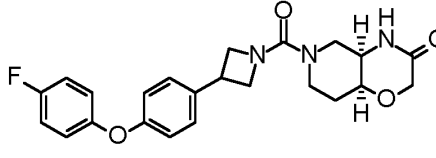
- 20 The following examples listed in Table 2 were prepared in analogy to the reaction methods described herein by using the indicated intermediates and commercial compounds

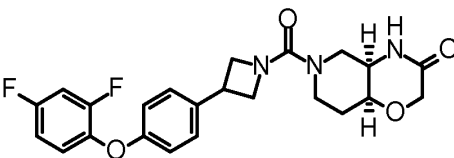
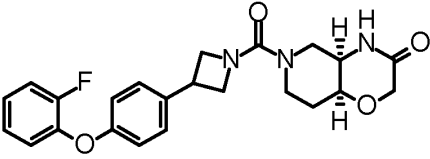
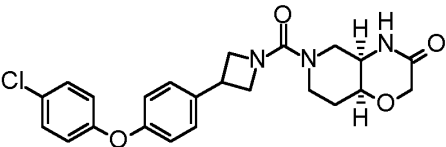
Table 2

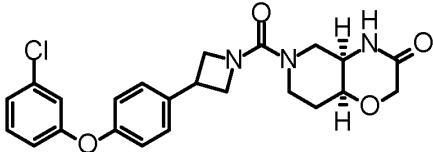
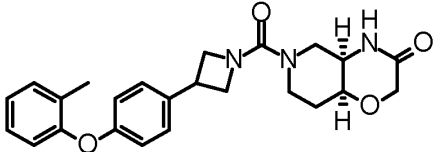
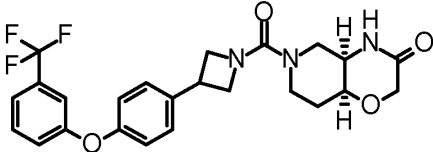
Ex.	Systematic Name / Structure	Building block	MS, m/z	Method
5	(+)-(4aR,8aS)-6-[3-[4-(4-Methylpyrimidin-2-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 2-Chloro-4-methylpyrimidine CAS RN 13036-57-2	424.4 [M+H] ⁺	A3
6	(+)-(4aR,8aS)-6-[3-(4-Pyridazin-3-yloxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 3-Chloropyridazine hydrochloride CAS RN 1120-95-2	410.1 [M+H] ⁺	A3
7	(+)-(4aR,8aS)-6-[3-[4-(4-Methyl-3-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 3-Fluoro-4-methylpyridine	423.1 [M+H] ⁺	A4

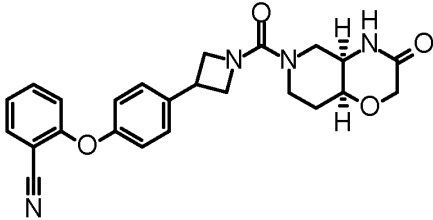
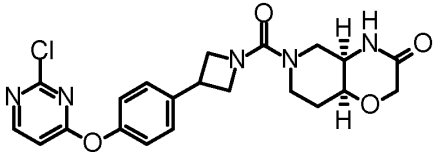
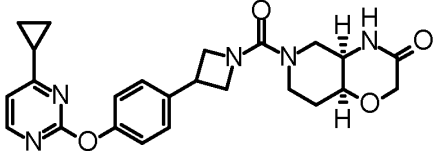
Ex.	Systematic Name / Structure	Building block	MS, m/z	Method
8	(+)-(4aR,8aS)-6-[3-[4-[(5-Fluoro-3-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 3,5-Difluoropyridine	427.1 [M+H] ⁺	A4
9	(+)-(4aR,8aS)-6-[3-[4-[(5-Chloro-3-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 3-Chloro-5-fluoropyridine	443.1 [M+H] ⁺	A4
10	(+)-(4aR,8aS)-6-[3-[4-(3-Pyridyloxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 3-Fluoropyridine	409.1 [M+H] ⁺	A4

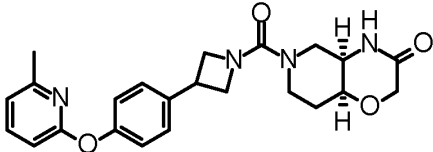
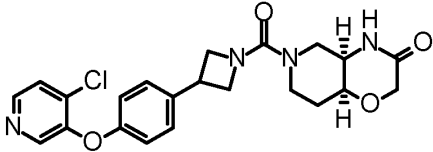
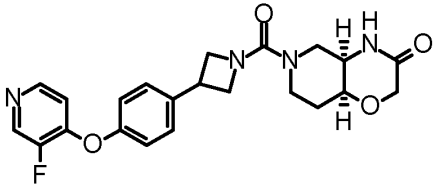
Ex.	Systematic Name / Structure	Building block	MS, m/z	Method
11	(+)-(4aR,8aS)-6-[3-[4-(4-Methylpyridazin-3-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 3-Chloro-4-methylpyridazine CAS RN 68206-04-2	424.5 [M+H]⁺	A3* *heated to 130°C
12	(+)-(4aR,8aS)-6-[3-[4-(3-Chloropyridazin-4-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 3,4-Dichloropyridazine CAS RN 1677-80-1	444.4 [M+H]⁺	A3
13	(+)-(4aR,8aS)-6-[3-[4-(4-Methoxypyrimidin-2-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 2-Chloro-4-methoxypyrimidine CAS RN 22536-63-6	440.4 [M+H]⁺	A3

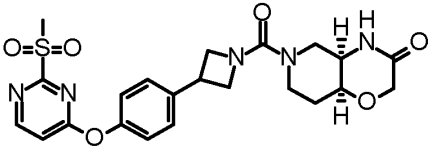
Ex.	Systematic Name / Structure	Building block	MS, m/z	Method
14	(+)-(4aR,8aS)-6-[3-[4-(4-(Trifluoromethyl)pyrimidin-2-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 2-Chloro-4-trifluoromethyl)pyrimidine CAS RN 33034-67-2	478.3 [M+H]⁺	A3
15	(+)-(4aR,8aS)-6-[3-[4-(3-Fluorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB4 and 3-Fluorophenol	426.2 [M+H]⁺	A2
16	(+)-(4aR,8aS)-6-[3-[4-(4-Fluorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB4 and 4-Fluorophenol	426.1 [M+H]⁺	A2

Ex.	Systematic Name / Structure	Building block	MS, m/z	Method
17	(+)-(4aR,8aS)-6-[3-[4-(2,4-Difluorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB4 and 2,4-Difluorophenol	444.1 [M+H] ⁺	A2
18	(+)-(4aR,8aS)-6-[3-[4-(2-fluorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB4 and 2-Fluorophenol	442.1 [M+H] ⁺	A2
19	(+)-(4aR,8aS)-6-[3-[4-(4-chlorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB4 and 4-Chlorophenol	426.1 [M+H] ⁺	A2

Ex.	Systematic Name / Structure	Building block	MS, m/z	Method
20	(+)-(4aR,8aS)-6-[3-[4-(3-Chlorophenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB4 and 3-Chlorophenol	442.1 [M+H] ⁺	A2
21	(+)-(4aR,8aS)-6-[3-[4-(2-Methylphenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB4 and 2-Methylphenol	422.2 [M+H] ⁺	A2
22	(+)-(4aR,8aS)-6-[3-[4-(3-(Trifluoromethyl)phenoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB4 and 3-Trifluoromethylphenol	476.2 [M+H] ⁺	A2

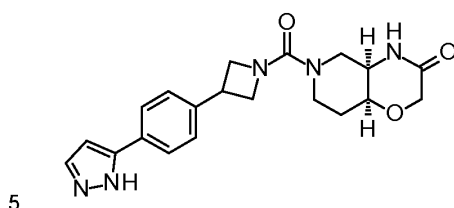
Ex.	Systematic Name / Structure	Building block	MS, m/z	Method
23	(+)-2-[4-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]phenoxy]benzonitrile 	BB3 and 2-Fluorobenzonitrile	433.2 [M+H] ⁺	A4* *stirred at 25°C no MW
24	(+)-(4aR,8aS)-6-[3-[4-(2-Chloropyrimidin-4-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 4-Bromo-2-chloro-pyrimidine CAS RN 885702-34-1	444.2 [M+H] ⁺	A3* *stirred at 25°C in DMF
25	(+)-(4aR,8aS)-6-[3-[4-(4-Cyclopropylpyrimidin-2-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 2-Chloro-4-cyclopropylpyrimidine CAS RN 954237-31-1	450.4 [M+H] ⁺	A3* *heated to 50°C in DMF

Ex.	Systematic Name / Structure	Building block	MS, m/z	Method
26	(+)-(4aR,8aS)-6-[3-[4-[(6-Methyl-2-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 2-Fluoro-6-methylpyridine	423.2 [M+H] ⁺	B1 step a)
27	(+)-(4aR,8aS)-6-[3-[4-[(4-chloro-3-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 4-Chloro-3-fluoropyridine	443.1 [M+H] ⁺	A4* *heated to 100°C
28	(+)-(4aR,8aS)-6-[3-[4-[(3-Fluoro-4-pyridyl)oxy]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 4-Chloro-3-fluoropyridine	427.1 [M+H] ⁺	A4* *heated to 100°C

Ex.	Systematic Name / Structure	Building block	MS, m/z	Method
29	(+)-(4aR,8aS)-6-[3-[4-(2-Methylsulfonylpyrimidin-4-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB3 and 4-Chloro-2-(methylsulfonyl)pyrimidine CAS RN 97229-11-3	488.1 [M+H] ⁺	A3* *stirred at 0°C in DMF

Example 31

(4aR,8aS)-6-[3-[4-(1H-Pyrazol-5-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



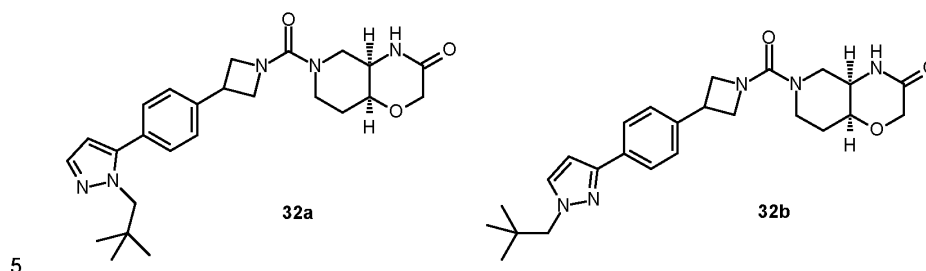
To a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (147.7 mg, 0.760 mmol; CAS RN 269410-08-4), (4aR,8aS)-6-[3-(4-bromophenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (BB4 step c, 200.0 mg, 0.510 mmol) and K₂CO₃ (140.22 mg, 1.01 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was added Pd(dppf)Cl₂ (66.12 mg, 0.100 mmol, CAS RN 12150-46-8) and the mixture was stirred at 90 °C for 12 h. The mixture was filtered and the filtrate evaporated. The residue was purified by prep-HPLC (0.225% v/v FA in water and ACN) to give the desired product (6.5 mg, 0.020 mmol, 3.3%) as an off-white solid. MS (ESI): m/z = 382.4 [M+H]⁺.

15 **Examples 32a and 32b**

- 65 -

(4aR,8aS)-6-[3-[4-[2-(2,2-Dimethylpropyl)pyrazol-3-yl]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one, and

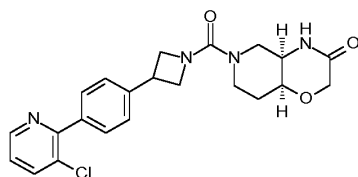
(4aR,8aS)-6-[3-[4-[1-(2,2-Dimethylpropyl)pyrazol-3-yl]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



The solution of (4aR,8aS)-6-[3-[4-(1H-pyrazol-5-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (example 31, 140.0 mg, 0.370 mmol), 1-bromo-2,2-dimethylpropane (110.88 mg, 0.730 mmol) and Cs₂CO₃ (239.18 mg, 0.730 mmol) in DMF (2.6 mL) was stirred at 80 °C for 12 h. The mixture was diluted with
 10 water and extracted three times with EtOAc (10 mL each). The combined organic layers were dried over Na₂SO₄, filtered and evaporated. The residue was purified and the regioisomers separated by prep-HPLC (0.225% v/v FA in water and ACN) to give the ex. HR1 (2.5 mg, 0.010 mmol, 2.6%) and ex. HR2 (31.4 mg, 0.070 mmol, 32.5%) each as a light yellow solid. MS (ESI): m/z =452.3 [M+H]⁺ for both regioisomers.

15 **Example 33**

(4aR, 8aS)-6-[3-[4-(3-Chloro-2-pyridyl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

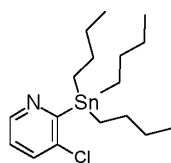


To a solution of tributyl-(3-chloro-2-pyridyl)stannane (122.5 mg, 0.300 mmol, CAS RN
 20 206357-78-0) and (4aR,8aS)-6-[3-(4-bromophenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (BB4 step c, 100.0 mg, 0.250 mmol) in DMF (5 mL) was added Pd(PPh₃)₄ (58.64 mg, 0.050 mmol) and the mixture was stirred at 100 °C

- 66 -

under N₂ atmosphere for 12 h. The mixture was poured into water (20 mL) and extracted three times with EtOAc (5 mL each). The combined organic layers were washed with brine and dried over Na₂SO₄, filtered and the filtrate evaporated. The residue was purified by reverse flash column chromatography (0.1% v/v FA in water and ACN) followed by
 5 prep-HPLC (0.225% v/v FA in water and ACN) to yield the desired compoundt as a white solid (2.8 mg, 99.4% purity, 2.6%). MS (ESI): m/z = 427.2 [M+H]⁺.

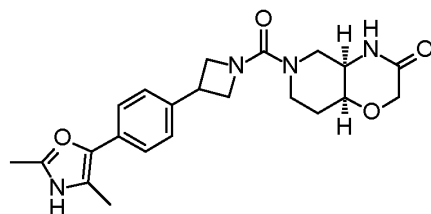
Step a) *Tributyl-(3-chloro-2-pyridyl)stannane*



To a solution of 2-bromo-3-chloropyridine (576.0 mg, 2.99 mmol, CAS RN 96424-68-9)
 10 in toluene (20 mL) under N₂ was added n-BuLi in hexane (2.5M, 1.32 mL, 3.29 mmol) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 2 h, followed by the addition of tributyltin chloride (1071.73 mg, 3.29 mmol). The reaction mixture was stirred for another 2 h at -78 °C, then warmed to RT and stirred for another 12h. The reaction was quenched with saturated aq. NH₄Cl solution (50 mL). The mixture was extracted three
 15 times with EtOAc (30 mL each), and the combined organic layers were washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated in vacuo to afford the desired product (1100 mg, 2.73 mmol, 91.3%) as light yellow oil which was used in the next step without further purification. MS (ESI): m/z = 404.1 [M+H]⁺.

Example 34

20 (4aR,8aS)-6-[3-[4-(2,4-Dimethyloxazol-5-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

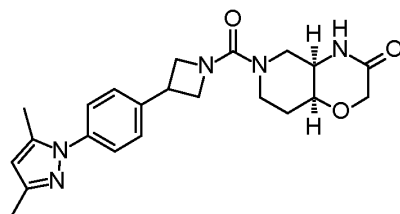


- 67 -

To a solution of (4aR,8aS)-6-[3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (BB4 step d, 80.0 mg, 0.180 mmol), Na₂CO₃ (38.42 mg, 0.360 mmol) and 5-bromo-2,4-dimethyl-oxazole (31.91 mg, 0.180 mmol, CAS RN 187399-73-1) in 1,4-dioxane (4 mL) and water (1 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (13.3 mg, 0.020 mmol) and the mixture was stirred at 100 °C under nitrogen atmosphere for 12 h. The mixture was poured into water (20 mL) and extracted three times with EtOAc (10 mL each). The combined organic layers were washed with brine and dried over Na₂SO₄, filtered and the filtrate concentrated. The residue was purified by prep-HPLC (0.5% ammonia in water and ACN) to furnish the desired compound as a pink solid (23.7 mg, 0.060 mmol, 30.6%). MS (ESI): m/z = 411.2 [M+H]⁺.

Example 35

(4aR,8aS)-6-[3-[4-(3,5-Dimethylpyrazol-1-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



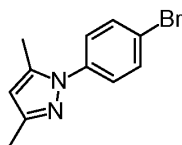
15

To a solution of 1-[4-(azetidin-3-yl)phenyl]-3,5-dimethyl-pyrazole (trifluoroacetic acid salt) (150.0 mg, 0.440 mmol) in ACN (5 mL) was added DIPEA (340.14 mg, 2.64 mmol) followed by (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (169.43 mg, 0.530 mmol, BB2a) and the reaction mixture was stirred at 80 °C for 12 h. The solution was concentrated, and the residue was purified by prep-HPLC (0.225% v/v TFA in water and ACN) to give the desired product as a light yellow solid (53.9 mg, 0.130 mmol, 27.7%, purity 92.4%). MS (ESI): m/z = 410.0 [M+H]⁺.

20

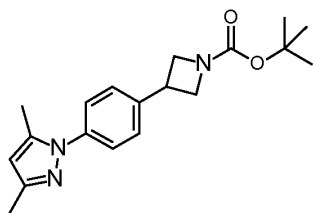
Step a) *1-(4-Bromophenyl)-3,5-dimethyl-pyrazole*

- 68 -



A solution of (4-bromophenyl)hydrazine (500.0 mg, 2.67 mmol, CAS RN 41931-18-4) and acetylacetone (294.41 mg, 2.94 mmol, CAS RN 123-54-6), copper(II) nitrate trihydrate (128.31 mg, 0.530 mmol, CAS RN 10031-43-3) in ACN (12 mL) was stirred at
 5 20°C for 2 h. The mixture was diluted with EtOAc (20 mL) and washed with water and then brine, the organic phase was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc = 20 : 1) to give the desired product as a light yellow oil (400 mg, 1.59 mmol, 71.2%). MS (ESI): m/z = 251.0 [M+H]⁺.

Step b) *tert*-Butyl 3-[4-(3,5-dimethylpyrazol-1-yl)phenyl]azetidine-1-carboxylate

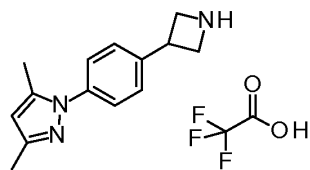


10

To a 40 mL vial equipped with a stirring bar was added *tert*-butyl 3-bromoazetidine-1-carboxylate (329.08 mg, 1.39 mmol, CAS RN 1064194-10-0), 1-(4-bromophenyl)-3,5-dimethyl-pyrazole (350.0 mg, 1.39 mmol, CAS RN 62546-27-4), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (7.81 mg, 0.010 mmol), NiCl₂·glyme (1.84 mg, 0.010 mmol),
 15 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (2.24 mg, 0.010 mmol), bis(trimethylsilyl)silyl-trimethyl-silane (346.57 mg, 1.39 mmol), Na₂CO₃ (295.45 mg, 2.79 mmol) and then DME (10 mL). The vial was sealed and placed under nitrogen. The reaction mixture was stirred and irradiated with a 34 W blue LED lamp (7 cm distance), with cooling fan to keep the reaction temperature at 25 °C for 14 h. The mixture was
 20 filtered and the filtrate was concentrated. The residue was purified by reversed flash column chromatography (0.1% v/v FA in water and ACN) to give the desired product as a yellow oil (300 mg, 0.920 mmol, 65.7%). MS (ESI): m/z = 328.1 [M+H]⁺.

Step c) *1*-[4-(Azetidin-3-yl)phenyl]-3,5-dimethyl-pyrazole, trifluoroacetic acid salt

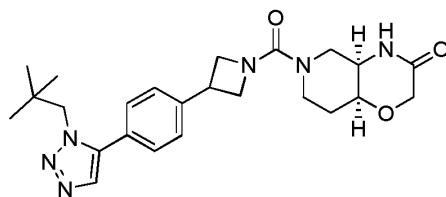
- 69 -



To a solution of tert-butyl 3-[4-(3,5-dimethylpyrazol-1-yl)phenyl]azetidine-1-carboxylate (150.0 mg, 0.460 mmol) in DCM (5 mL) was added TFA (1.0 mL). The mixture was stirred at 20 °C for 3 h and then concentrated to give the crude desired product (150 mg, 0.440 mmol, 95.9%) as a yellow oil. MS (ESI): $m/z = 228.1$ $[M+H]^+$.

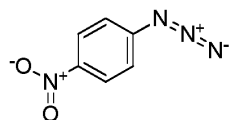
Example 36

(4aR, 8aS)-6-[3-[4-[3-(2,2-Dimethylpropyl)triazol-4-yl]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



A mixture of (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (66.2 mg, 0.210 mmol, BB2a), DIPEA (241.9 mg, 1.87 mmol) and 5-[4-(azetidin-3-yl)phenyl]-1-(2,2-dimethylpropyl)triazole trifluoroacetic acid salt (72.0 mg, 0.190 mmol) in ACN (3 mL) was stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (0.025 % FA in water and ACN) to give the desired compound as a light yellow solid (18 mg, 0.040 mmol, 20.5%). MS (ESI): $m/z = 453.0$ $[M+H]^+$.

Step a) *1-Azido-4-nitro-benzene*

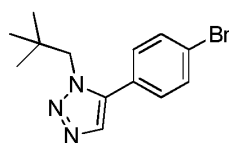


4-Nitroaniline (2000.0 mg, 14.48 mmol) was dissolved in ACN (20 mL), and the mixture was cooled to 0 °C in an ice-salt bath. To the stirred solution was added tert-butyl nitrite (1791.8 mg, 17.38 mmol) and the mixture was stirred for 10 min. Then

- 70 -

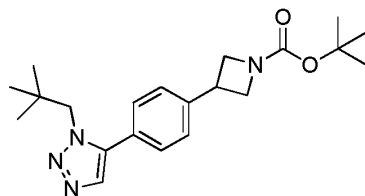
azidotrimethylsilane (2.88 mL, 21.72 mmol) was added dropwise, and the resulting brown solution was stirred at 25 °C for 2 h. The reaction mixture was poured into water (100 mL) and extracted three times with EtOAc (100 mL each) and the organic layer was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (100% PE) to give 1-azido-4-nitro-benzene (2100 mg, 12.64 mmol, 87.3) as yellow solid.

Step b) *5-(4-Bromophenyl)-1-(2,2-dimethylpropyl)triazole*



To the solution of 4'-bromoacetophenone (1940.4 mg, 9.75 mmol), neopentylamine (1104.6 mg, 12.67 mmol), 1-azido-4-nitro-benzene (1600.0 mg, 9.75 mmol), AcOH (175.6 mg, 2.92 mmol) in toluene (64 mL) were added molecular sieves (4Å, 500 mg) and the reaction was stirred at 100 °C for 16 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was by column chromatography (PE : EA = 3 : 1) to give the desired compound as a yellow gum (997 mg, 3.39 mmol, 34.8%).

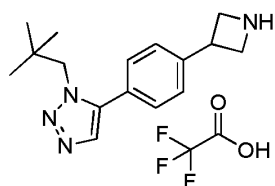
Step c) *tert-Butyl 3-[4-[3-(2, 2-dimethylpropyl) triazol-4-yl] phenyl] azetidine-1-carboxylate*



The title compound was prepared in analogy to example 35, step b), from 5-(4-bromophenyl)-1-(2,2-dimethylpropyl)triazole and tert-butyl 3-bromoazetidine-1-carboxylate. Yellow gum (75.9%). MS (ESI): $m/z = 371.0$ $[M+H]^+$.

Step d) *5-[4-(Azetidin-3-yl) phenyl]-1-(2, 2-dimethylpropyl) triazole trifluoroacetic acid salt*

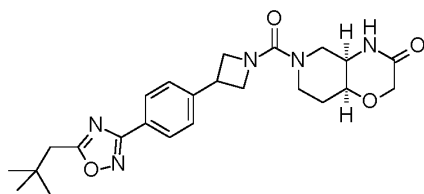
- 71 -



To a solution of tert-butyl 3-[4-[3-(2,2-dimethylpropyl)triazol-4-yl]phenyl]azetidine-1-carboxylate (70.0 mg, 0.190 mmol) in DCM (2 mL) was added TFA (0.5 mL). The mixture was stirred at 20 °C for 12 h and then evaporated under reduced pressure to give the crude desired compound as a yellow oil (72 mg, 0.190 mmol, 99.1%). MS (ESI): m/z = 270.9 $[M+H]^+$.

Example 37

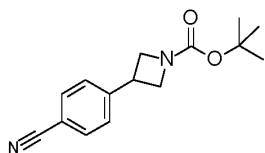
(4aR,8aS)-6-[3-[4-[5-(2,2-Dimethylpropyl)-1,2,4-oxadiazol-3-yl]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



10

To a solution of 3-[4-(azetidin-3-yl)phenyl]-5-(2,2-dimethylpropyl)-1,2,4-oxadiazole, trifluoroacetic acid salt (150.0 mg, 0.390 mmol) in ACN (4 mL) was added DIPEA (301.3 mg, 2.34 mmol) and (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (150.07 mg, 0.470 mmol, BB2a) and the reaction was stirred at 80 °C for 12 h. The reaction mixture was evaporated and the residue was purified by prep-HPLC (0.225% v/v FA in water and ACN) to give the desired product as a light yellow solid (54.4 mg, 0.120 mmol, 30.4%). MS (ESI): m/z = 454.4 $[M+H]^+$.

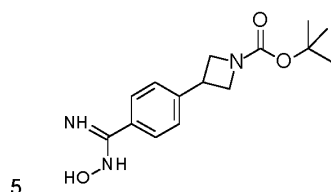
Step a) *tert*-Butyl 3-(4-Cyanophenyl)azetidine-1-carboxylate



- 72 -

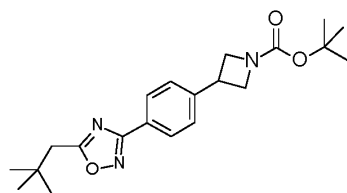
The title compound was prepared in analogy to example 35, step b), from 4-bromobenzonitrile and tert-butyl 3-bromoazetidine-1-carboxylate. Light brown oil (1976 mg, 7.65 mmol, 69.6%). MS (ESI): $m/z = 203.6 [M-56+H]^+$.

Step b) *tert-Butyl 3-[4-(N-hydroxycarbamimidoyl)phenyl]azetidine-1-carboxylate*



A solution of hydroxylamine hydrochloride (349.7 mg, 5.03 mmol) in EtOH (8 mL) was added Na_2CO_3 (266.7 mg, 2.52 mmol) in water (2 mL) and the mixture was stirred at 20 °C for 25 min. Then tert-butyl 3-(4-cyanophenyl)azetidine-1-carboxylate (1000.0 mg, 3.87 mmol) was added and the mixture was stirred at 95 °C for 12 h. The mixture was diluted
10 with water, concentrated under vacuum to remove the EtOH, the residue was partitioned between EtOAc (100 mL) and water (100 mL) and was extracted three times with water. The organic layer was washed with saturated NaCl solution (50 mL), dried over Na_2SO_4 and evaporated to give the desired product as a light yellow oil (773 mg, 2.65 mmol, 68.5%). MS (ESI): $m/z = 292.5 [M+H]^+$.

15 Step c) *tert-Butyl 3-[4-[5-(2,2-Dimethylpropyl)-1,2,4-oxadiazol-3-yl]phenyl]azetidine-1-carboxylate*

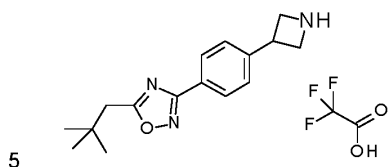


To a solution of tert-butyl 3-[4-(N-hydroxycarbamimidoyl)phenyl]azetidine-1-carboxylate (770.0 mg, 2.64 mmol) and DIPEA (1.41 mL, 7.93 mmol) in toluene (6 mL) was added
20 3,3-dimethylbutyryl chloride (426.9 mg, 3.17 mmol) at 0 °C, the mixture was stirred at 25 °C for 10 min. and then warmed up to 80 °C and stirred for 12 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (PE : EA =

- 73 -

10 : 1) to give the desired product (620 mg, 1.67 mmol, 63.2%) as a light brown oil. MS (ESI): $m/z = 316.5$ $[M-56+H]^+$.

Step d) 3-[4-(Azetidin-3-yl)phenyl]-5-(2,2-dimethylpropyl)-1,2,4-oxadiazole (trifluoroacetic acid salt)

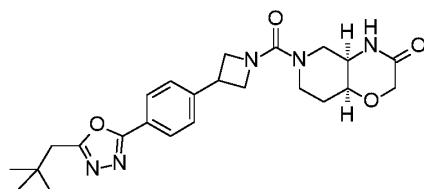


To a solution of tert-butyl 3-[4-[5-(2,2-dimethylpropyl)-1,2,4-oxadiazol-3-yl]phenyl]azetidine-1-carboxylate (300.0 mg, 0.810 mmol) in DCM (3 mL) was added TFA (0.6 mL, 7.79 mmol) and the mixture was stirred at 20 °C for 12 h. The mixture was evaporated to yield the crude desired product as a light yellow oil (300 mg, 0.780 mmol, 96.4%). MS (ESI): $m/z = 272.6$ $[M+H]^+$.

10

Example 38

(4aR,8aS)-6-[3-[4-[5-(2,2-Dimethylpropyl)-1,3,4-oxadiazol-2-yl]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

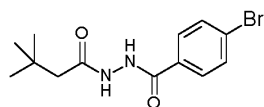


15 To a solution of 2-[4-(azetidin-3-yl)phenyl]-5-(2,2-dimethylpropyl)-1,3,4-oxadiazole trifluoroacetic acid salt (100.0 mg, 0.260 mmol) in ACN (2.5 mL) was added DIPEA (200.8 mg, 1.56 mmol) and (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (100.04 mg, 0.310 mmol, BB2a) and the reaction was stirred at 80 °C for 12 h. The reaction mixture was evaporated and the residue was purified by prep-HPLC (0.225% v/v FA in water and ACN) to give the desired product (48.3 mg, 0.110 mmol, 40.6%) as a light yellow solid. MS (ESI): $m/z = 454.3$ $[M+H]^+$.

20

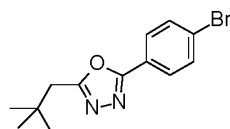
Step a) 4-Bromo-N'-(3,3-dimethylbutanoyl)benzoic hydrazide

- 74 -



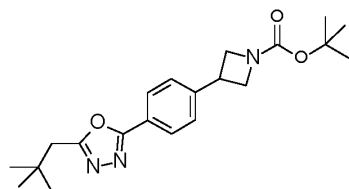
To a solution of 4-bromobenzoic hydrazide (5.0 g, 23.25 mmol, CAS RN 5933-32-4) and DIPEA (12.4 mL, 69.75 mmol, CAS RN 7087-68-5) in DCM (50 mL) was added 3,3-dimethylbutyryl chloride (3.76 g, 27.9 mmol, CAS RN 122-94-1) at 0 °C and the mixture
 5 was allowed to warm to 20 °C. After stirring for 12 h the mixture was diluted by water, extracted three times with EtOAc (200 mL each) and the combined organic layers were washed three times with water (100 mL each). The combined organic layers were dried over Na₂SO₄, filtered and evaporated to give the desired product as a light yellow solid (7 g, 22.4 mmol, 96.1%). MS (ESI): m/z = 315.4 [M+H]⁺.

10 Step b) 2-(4-Bromophenyl)-5-(2,2-dimethylpropyl)-1,3,4-oxadiazole



To a solution of 4-bromo-N'-(3,3-dimethylbutanoyl)benzoic hydrazide (5000.0 mg, 16.0 mmol) in toluene (102 mL) was added TsOH (5498.3 mg, 31.9 mmol) and the mixture was stirred at 110 °C for 12 h. The mixture was concentrated and the residue was purified by
 15 silica gel chromatography eluting with PE : EtOAc (10 : 1) to give the desired product as a light yellow solid (1000 mg, 3.4 mmol, 21.2%). MS (ESI): m/z = 295.4 [M+H]⁺.

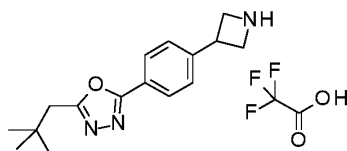
Step c) *tert*-Butyl 3-[4-[5-(2,2-dimethylpropyl)-1,3,4-oxadiazol-2-yl]phenyl]azetidine-1-carboxylate



20 The title compound was prepared in analogy to example 35, step b), from 2-(4-bromophenyl)-5-(2,2-dimethylpropyl)-1,3,4-oxadiazole and *tert*-butyl 3-bromoazetidine-1-carboxylate. Light brown oil. MS (ESI): m/z = 372.5 [M+H]⁺.

- 75 -

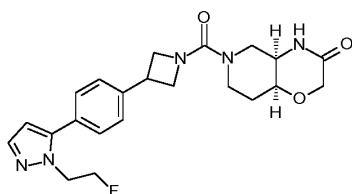
Step d) 2-[4-(Azetidin-3-yl)phenyl]-5-(2,2-dimethylpropyl)-1,3,4-oxadiazole
(trifluoroacetic acid salt)



To a solution of tert-butyl 3-[4-[5-(2,2-dimethylpropyl)-1,3,4-oxadiazol-2-yl]phenyl]azetidine-1-carboxylate (200.0 mg, 0.540 mmol) in DCM (2 mL) was added TFA (0.4 mL) and the mixture was stirred at 20 °C for 12 h. The mixture was evaporated to give the crude desired product as a light brown oil (201 mg, 0.520 mmol, 96.9%). MS (ESI): $m/z = 272.6 [M+H]^+$.

Example 39

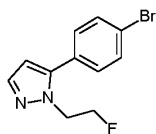
(4a*R*,8a*S*)-6-[3-[4-[2-(2-fluoroethyl)pyrazol-3-yl]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one



To a solution of 5-[4-(azetidin-3-yl)phenyl]-1-(2-fluoroethyl)pyrazole (110 mg, 0.380 mmol) and (4-nitrophenyl) (4a*R*,8a*S*)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-*b*][1,4]oxazine-6-carboxylate (124 mg, 0.390 mmol, BB2a) in MeCN (6 mL) was added *N,N*-diisopropylethylamine (0.2 mL, 1.15 mmol) with stirring at 60 °C. The solution was stirred at 60 °C for 16 h. The solution was concentrated under vacuum to give a residue, which was purified by HPLC (TFA conditions) to give (4a*R*,8a*S*)-6-[3-[4-[2-(2-fluoroethyl)pyrazol-3-yl]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one (80 mg, 45%) as white solid. MS (ESI): $m/z = 428.4 [M+H]^+$.

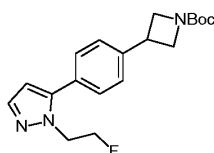
Step a) 5-(4-Bromophenyl)-1-(2-fluoroethyl)pyrazole

- 76 -



To a stirred solution at 20 °C of 2-fluoroethylhydrazine (330 mg, 4.23 mmol, CAS RN 126889-84-7) in DMF (20 mL) was added (*E*)-1-(4-bromophenyl)-3-(dimethylamino)prop-2-en-1-one (752 mg, 2.96 mmol, CAS RN 849619-11-0). The
 5 resulting mixture was stirred at 25 °C for 1 h and then at 70 °C for 5 h. The solution was concentrated under vacuum to give a residue, which was purified by flash column chromatography (petroleum ether:EtOAc 3:1) to give 5-(4-bromophenyl)-1-(2-fluoroethyl)pyrazole (450 mg, 39%) as white solid. MS (ESI): $m/z = 269.0/271.0$ $[M+H]^+$.

Step b) *tert*-Butyl 3-[4-[2-(2-fluoroethyl)pyrazol-3-yl]phenyl]azetidine-1-carboxylate

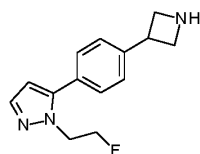


10

tert-Butyl 3-bromoazetidine-1-carboxylate (395 mg, 1.67 mmol, CAS RN 1064194-10-0), 5-(4-bromophenyl)-1-(2-fluoroethyl)pyrazole (450 mg, 1.67
 mmol), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (19 mg, 0.020 mmol, CAS RN 870987-63-6), dichloronickel 1,2-dimethoxyethane (2.0 mg, 0.010 mmol), 4-*tert*-butyl-2-(4-*tert*-butyl-
 15 2-pyridyl)pyridine (3.0 mg, 0.010 mmol), *bis*(trimethylsilyl)silyltrimethyl-silane (416 mg, 1.67 mmol) and sodium carbonate (355 mg, 3.35 mmol) were mixed in DME (15 mL). The reaction mixture was stirred and irradiated with a 34 W blue LED lamp (7 cm away), with cooling fan to keep the reaction temperature at 25 °C for 14 h. The solution was poured into brine (30 mL) and extracted with EtOAc (20 mL). The organic layer was
 20 concentrated under vacuum to give a residue, which was purified by Prep-TLC (petroleum ether:EtOAc 1:1) to give *tert*-butyl 3-[4-[2-(2-fluoroethyl)pyrazol-3-yl]phenyl]azetidine-1-carboxylate (450 mg, 69%) as light yellow oil MS (ESI): $m/z = 346.1$ $[M+H]^+$.

Step c) 5-[4-(Azetidin-3-yl)phenyl]-1-(2-fluoroethyl)pyrazole

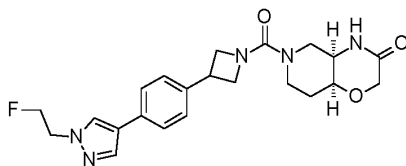
- 77 -



A solution of *tert*-butyl 3-[4-[2-(2-fluoroethyl)pyrazol-3-yl]phenyl]azetidine-1-carboxylate (160 mg, 0.410 mmol) in HCl in MeOH (4.0 mL, 16 mmol) was stirred at 25 °C for 4 h. The solution was concentrated under vacuum to give 5-[4-(azetidin-3-yl)phenyl]-1-(2-fluoroethyl)pyrazole (110 mg, 92%) as light yellow oil, which was used with no further purification in the next step. MS (ESI): $m/z = 246.1$ $[M+H]^+$.

Example 40

(4aR,8aS)-6-[3-[4-[1-(2-Fluoroethyl)pyrazol-4-yl]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



10

A mixture of 1-(2-fluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (58 mg, 0.24 mmol, CAS RN 1049730-39-3), (4aR,8aS)-6-(3-(4-bromophenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (BB4 step c, 80 mg, 0.20 mmol), K_2CO_3 (2.0 mg, 0.02 mmol), Cs_2CO_3 (198 mg, 0.610 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (15 mg, 0.02 mmol) in DMSO (4 mL) and H_2O (0.5 mL) was stirred under nitrogen atmosphere at 80 °C for 16 h. The mixture was filtered and then purified by prep-HPLC (basic condition) to give the title compound as a grey solid (41 mg, 44%). LC-MS: 428.2 $[M+H]^+$.

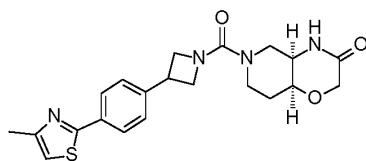
15

Example 41

(4aR,8aS)-6-[3-[4-(4-Methyl-1,3-thiazol-2-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

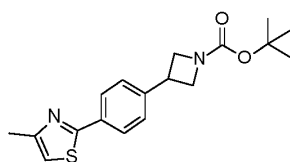
20

- 78 -



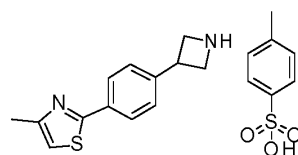
The title compound was prepared in analogy to example 31, intermediate, from 4-nitrophenyl (4aR,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate and 2-(4-(azetidin-3-yl)phenyl)-4-methylthiazole 4-methylbenzenesulfonate. Colorless
5 foam (37%). MS (ESI): $m/z = 413.3 [M+H]^+$.

Step a) *tert*-Butyl 3-(4-(4-methylthiazol-2-yl)phenyl)azetidine-1-carboxylate



The title compound was prepared in analogy to BB4, step a), from 4-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiazole (Maybridge) and *tert*-butyl 3-iodoazetidine-1-carboxylate (CAS RN 254454-54-1). Colorless oil which was used in the
10 next step without further purification. MS (ESI): $m/z = 331.2 [M+H]^+$.

Step b) 2-[4-(Azetidin-3-yl)phenyl]-4-methyl-thiazole; 4-methylbenzenesulfonic acid

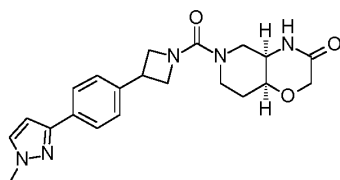


A suspension of *tert*-butyl 3-(4-(4-methylthiazol-2-yl)phenyl)azetidine-1-carboxylate (28
15 mg, 84.7 μmol) and 4-methylbenzenesulfonic acid hydrate (19.3 mg, 102 μmol) in EtOAc (0.3 mL) were stirred at reflux for 2 h. The mixture was completely evaporated to provide the desired compound which was used in the next step without further purification. MS (ESI): $m/z = 231.1 [M+H]^+$.

Example 42

- 79 -

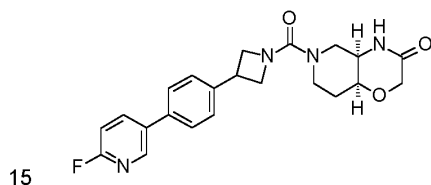
(4aR,8aS)-6-[3-[4-(1-Methylpyrazol-3-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



(4aR,8aS)-6-(3-(4-Bromophenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (16 mg, 40.6 μ mol, BB4, step c) and (1-methyl-1H-pyrazol-3-yl)boronic acid (5.11 mg, 40.6 μ mol, CAS RN 869973-96-6), and tetrakis(triphenylphosphine)palladium(0) (2.34 mg, 2.03 μ mol) were dissolved in THF (600 μ L) and water (60 μ L) and the reaction stirred at 80°C over night. The reaction mixture was extracted with EtOAc and H₂O, the organic layer dried over Na₂SO and evaporated. The crude product was purified by a prep-HPLC to give the compound as a white solid. MS (ESI): m/z = 396.2 [M+H]⁺.

Example 43

(4aR,8aS)-6-[3-[4-(6-Fluoropyridin-3-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

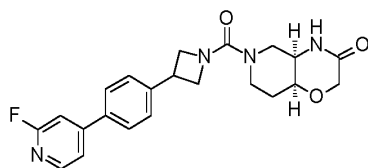


The title compound was prepared in analogy to example 42, from (4aR,8aS)-6-(3-(4-bromophenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (BB4, step c) and 2-fluoropyridine-5-boronic acid (CAS RN: 351019-18-6). White solid. MS (ESI): m/z = 411.2 [M+H]⁺.

Example 44

(4aR,8aS)-6-[3-[4-(2-Fluoropyridin-4-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

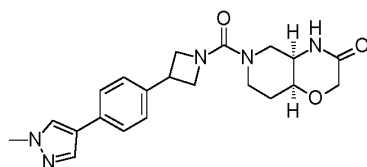
- 80 -



The title compound was prepared in analogy to example 42, from (4aR,8aS)-6-(3-(4-bromophenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (BB4, step c) and (2-fluoropyridin-4-yl)boronic acid (CAS RN: 401815-98-3). Yellow powder (84%). MS (ESI): $m/z = 411.2$ $[M+H]^+$.

Example 45

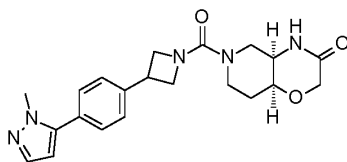
(4aR,8aS)-6-[3-[4-(1-Methylpyrazol-4-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



The title compound was prepared in analogy to example 42, from (4aR,8aS)-6-(3-(4-bromophenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (BB4, step c) and 1-methyl-1H-pyrazole-4-boronic acid (CAS RN: 763120-58-7). Light yellow powder (57%). MS (ESI): $m/z = 396.2$ $[M+H]^+$.

Example 46

(4aR,8aS)-6-[3-[4-(2-Methylpyrazol-3-yl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



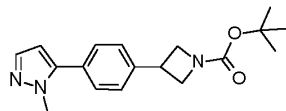
The title compound was prepared in analogy to example 31, intermediate, from 4-nitrophenyl (4aR,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate

- 81 -

and 5-(4-(azetidin-3-yl)phenyl)-1-methyl-1H-pyrazole 4-methylbenzenesulfonate.

Colorless solid (25%). MS (ESI): $m/z = 396.2$ $[M+H]^+$.

Step a) *tert*-Butyl 3-[4-(2-methylpyrazol-3-yl)phenyl]azetidine-1-carboxylate



- 5 The title compound was prepared in analogy to example BB4, step a, from *tert*-butyl 3-iodoazetidine-1-carboxylate (CAS RN 254454-54-1) and (4-(1-methyl-1H-pyrazol-5-yl)phenyl)boronic acid (ChemBridge Corp.). Colorless oil which was used in the next step without further purification. MS (ESI): $m/z = 314.3$ $[M+H]^+$.

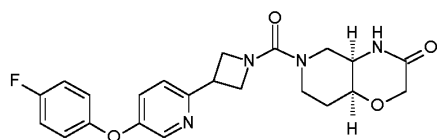
Step b) 5-[4-(Azetidin-3-yl)phenyl]-1-methyl-pyrazole; 4-methylbenzenesulfonic acid

- 10 The title compound was prepared in analogy to example 41, step b, from *tert*-butyl 3-[4-(2-methylpyrazol-3-yl)phenyl]azetidine-1-carboxylate. Light brown gum. MS (ESI): $m/z = 214.1$ $[M+H]^+$.

Example 47

(4aR,8aS)-6-[3-[5-(4-Fluorophenoxy)-2-pyridyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-

- 15 hexahydropyrido[4,3-b][1,4]oxazin-3-one



To a solution of 2-(azetidin-3-yl)-5-(4-fluorophenoxy)pyridine (50 mg, 0.17 mmol) and DIPEA (0.17 mL, 1.04 mmol) in ACN (2 mL) was added (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (67 mg, 0.21 mmol,

- 20 BB2a) at 25 °C. The mixture was stirred at 90 °C for 12 h, concentrated under reduced pressure, purified by preparative HPLC (0.225% TFA) and lyophilized to give the title compound (22.1 mg, 0.050 mmol, 28.5% yield) as light yellow solid. MS (ESI): $m/z = 427.2$ $[M+H]^+$.

Step a) *tert*-Butyl 3-[5-(4-fluorophenoxy)-2-pyridyl]-3-hydroxy-azetidine-1-carboxylate

- 82 -

2-Bromo-5-(4-fluorophenoxy)pyridine (350 mg, 1.31 mmol, CAS RN 1643917-85-4) was dissolved in toluene (15 mL) and cooled to -78 °C. nBuLi in hexanes (0.57 mL, 1.44 mmol) was added dropwise and the mixture was stirred at -78 °C for 30 minutes under a N₂ atmosphere. 1-Boc-3-azetidinone (246 mg, 1.44 mmol, CAS RN 398489-26-4) in toluene (2 mL) was added. The reaction mixture was stirred at 0 °C for 4 h, quenched with saturated NH₄Cl (20 mL) and extracted with EtOAc (2 x 15 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, concentrated in vacuo and purified by reverse phase flash chromatography to give the title compound (171 mg, 0.470 mmol, 36.3% yield) as white solid. MS (ESI): m/z = 361.2 [M+H]⁺.

10 Step b) *tert-Butyl 3-chloro-3-[5-(4-fluorophenoxy)-2-pyridyl]azetidine-1-carboxylate*

To a solution of *tert*-butyl 3-[5-(4-fluorophenoxy)-2-pyridyl]-3-hydroxy-azetidine-1-carboxylate (500 mg, 1.39 mmol) in DCM (15 mL) was added thionyl chloride (990 mg, 8.32 mmol) at 0° C. The mixture was stirred at 20 °C for 12 h, poured into sat. Na₂CO₃ (15 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, concentrated in vacuo and purified by reverse phase flash chromatography (0.05% TFA) to give the title compound (230 mg, 0.610 mmol, 43.8% yield) as light yellow oil. MS (ESI): m/z = 322.8 [M-C₄H₈+H]⁺.

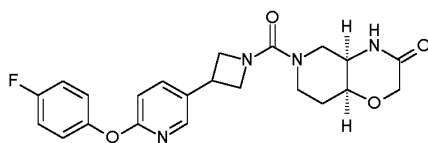
Step c) *2-(Azetidin-3-yl)-5-(4-fluorophenoxy)pyridine*

To a solution of *tert*-butyl 3-chloro-3-[5-(4-fluorophenoxy)-2-pyridyl]azetidine-1-carboxylate (200 mg, 0.530 mmol) and formic acid (121 mg, 2.64 mmol) in methanol (12 mL) was added wet Pd/C (100 mg, 0.530 mmol). The mixture was stirred at 50 °C for 12 h and filtered. The filtrate was concentrated in vacuum to give a yellow residue, which was purified by reverse phase flash chromatography (0.05% TFA) to give the title compound (50 mg, 0.200 mmol, 38.8% yield) as colorless oil and *tert*-butyl 3-[5-(4-fluorophenoxy)-2-pyridyl]azetidine-1-carboxylate (54 mg, 0.160 mmol, 29.7% yield) as light brown oil. MS (ESI): m/z = 245.2 [M+H]⁺.

Example 48

(4aR,8aS)-6-(3-(6-(4-Fluorophenoxy)pyridin-3-yl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one

- 83 -



A solution of (4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (2S,3S)-2,3-bis((4-methylbenzoyl)oxy)succinate (54.3 mg, 100 μ mol) and di(1H-1,2,4-triazol-1-yl)methanone (16 mg, 100 μ mol) in ACN (2 mL) and TEA (73 mg, 100 μ L, 717 μ mol) was shaken for 90 min at room temperature. 5-(Azetidin-3-yl)-2-(4-fluorophenoxy)pyridine 4-methylbenzenesulfonate (42 mg, 0.1 mmol) was added and the mixture was shaken for 30 min at room temperature and subsequently for 90 min at 60 $^{\circ}$ C. The clear solution was filtered through a Hypersep Amino SPE Column (1 g, Part. No.: 60108-432). The column was washed with ACN (total 6 mL), the solvent was removed under reduced pressure and the residue purified by prep. HPLC to obtain the title compound (15 mg, 35.4 μ mol, 35.4 % yield) as colorless waxy solid. MS (ESI): m/z = 427.2 $[M+H]^+$.

Step a) *tert*-Butyl 3-(6-phenoxy)pyridin-3-yl)azetidine-1-carboxylate

DME (6 mL) was added to a mixture of 5-bromo-2-(4-fluorophenoxy)pyridine (686 mg, 2.56 mmol, CAS RN 936343-65-6), *tert*-butyl 3-bromoazetidine-1-carboxylate (604 mg, 2.56 mmol, CAS RN 1064194-10-0), (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆ (29 mg, 25.6 μ mol, CAS RN 870987-63-6), tris(trimethylsilyl)silane (636 mg, 789 μ L, 2.56 mmol) and anhydrous sodium carbonate (407 mg, 3.84 mmol). The mixture was stirred for 5 min with argon bubbling through the suspension. The reaction vessel was sealed. A separate vial was charged with Nickel(II) chloride ethylene glycol dimethyl ether complex (2.8 mg, 12.8 μ mol, CAS RN 29046-78-4) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (3.4 mg, 12.8 μ mol). DME (616 μ L) was added. The vial was sealed, purged with argon, sonicated for 5 min and then poured into the reaction vessel. The reaction mixture was stirred and irradiated with a 420 nm lamp under an argon atmosphere for 3 hours. The solid was filtered off, washed with ethyl acetate and the filtrate was evaporated. The crude was absorbed with isolute HM-N, dried and purified by flash chromatography to give the title compound (296 mg, 774 μ mol, 30.2 % yield) as light yellow waxy solid. MS (ESI): m/z = 361.2 $[M+H]^+$.

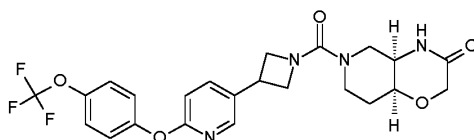
Step b) 5-(Azetidin-3-yl)-2-(4-fluorophenoxy)pyridine 4-methylbenzenesulfonate

- 84 -

To a solution of *tert*-butyl 3-(6-phenoxy)pyridin-3-yl)azetidine-1-carboxylate (296 mg, 907 μmol) in ethyl acetate (7 mL) was added 4-methylbenzenesulfonic acid hydrate (77 mg, 407 μmol). The mixture was heated under reflux conditions for 18 h, cooled to room temperature, diluted with 3 mL diethyl ether, stirred for 1 h and filtered. The solid was washed with ether (3 x 1 mL) and dried under vacuum to obtain the title compound (285 mg, 684 μmol , 75.4 % yield) as white crystals. MS (ESI): $m/z = 245.1$ $[\text{M}+\text{H}]^+$.

Example 49

(4aR,8aS)-6-(3-(6-(4-(Trifluoromethoxy)phenoxy)pyridin-3-yl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one



10

In analogy to the procedure described in example 48, (4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (2S,3S)-2,3-bis((4-methylbenzoyl)oxy)succinate was reacted with 5-(azetidin-3-yl)-2-(4-(trifluoromethoxy)phenoxy)pyridine 4-methylbenzenesulfonate to obtain the title compound as white foam. MS (ESI): $m/z = 493.2$ $[\text{M}+\text{H}]^+$.

15 Step a) *tert*-Butyl 3-(6-(4-(trifluoromethoxy)phenoxy)pyridin-3-yl)azetidine-1-carboxylate

In analogy to the procedure described in example 48 a, 5-bromo-2-(4-(trifluoromethoxy)phenoxy)pyridine (CAS RN 909849-01-0) was reacted with *tert*-butyl 3-bromoazetidine-1-carboxylate to give the title compound as light yellow waxy solid. MS (ESI): $m/z = 411.2$ $[\text{M}+\text{H}]^+$.

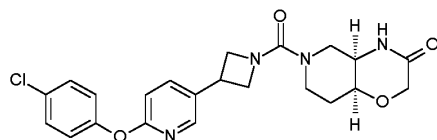
20 Step b) 5-(Azetidin-3-yl)-2-(4-(trifluoromethoxy)phenoxy)pyridine 4-methylbenzenesulfonate

In analogy to the procedure described in example 48 b, *tert*-butyl 3-(6-(4-(trifluoromethoxy)phenoxy)pyridin-3-yl)azetidine-1-carboxylate was reacted with 4-methylbenzenesulfonic acid hydrate to obtain the title compound as white crystals. MS

25 (ESI): $m/z = 311.1$ $[\text{M}+\text{H}]^+$.

Example 50

(4aR,8aS)-6-(3-(6-(4-Chlorophenoxy)pyridin-3-yl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one



In analogy to the procedure described in example 48, (4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (2S,3S)-2,3-bis((4-methylbenzoyl)oxy)succinate was reacted with 5-(azetidin-3-yl)-2-(4-chlorophenoxy)pyridine 4-methylbenzenesulfonate to obtain the title compound as white foam. MS (ESI): $m/z = 443.2 [M+H]^+$.

Step a) *tert*-Butyl 3-(6-(4-chlorophenoxy)pyridin-3-yl)azetidine-1-carboxylate

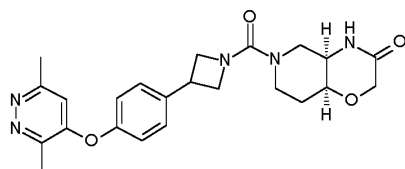
In analogy to the procedure described in example 48 a, 5-bromo-2-(4-chlorophenoxy)pyridine (CAS RN 28231-69-8) was reacted with *tert*-butyl 3-bromoazetidine-1-carboxylate to give the title compound as off-white solid. MS (ESI): $m/z = 361.2 [M+H]^+$.

Step b) 5-(Azetidin-3-yl)-2-(4-chlorophenoxy)pyridine 4-methylbenzenesulfonate

In analogy to the procedure described in example 48 b, *tert*-butyl 3-(6-(4-chlorophenoxy)pyridin-3-yl)azetidine-1-carboxylate was reacted with 4-methylbenzenesulfonic acid hydrate to obtain the title compound as white crystals. MS (ESI): $m/z = 261.1 [M+H]^+$.

Example 51

(4aR,8aS)-6-[3-[4-(3,6-Dimethylpyridazin-4-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



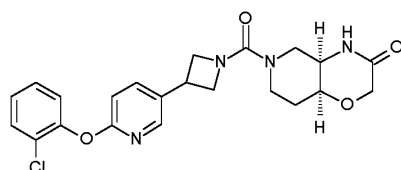
A mixture of (4aR,8aS)-6-(3-(4-hydroxyphenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (50 mg, 151 μ mol, BB3), 4-chloro-3,6-

- 86 -

dimethylpyridazine (23.7 mg, 166 μ mol, CAS RN 68206-05-3) and K_2CO_3 (41.7 mg, 302 μ mol) in DMSO (0.5 mL) was stirred in a sealed tube for 14 h at ambient temperature and purified by reverse phase flash chromatography to give the title compound (20 mg, 30%) as off-white solid. MS (ESI): m/z = 438.3 $[M+H]^+$.

5 **Example 52**

(4aR,8aS)-6-(3-(6-(2-Chlorophenoxy)pyridin-3-yl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one



In analogy to the procedure described in example 48, (4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (2S,3S)-2,3-bis((4-methylbenzoyl)oxy)succinate was reacted with 5-(azetidin-3-yl)-2-(2-chlorophenoxy)pyridine 4-methylbenzenesulfonate to obtain the title compound as off-white solid. MS (ESI): m/z = 443.3 $[M+H]^+$.

Step a) *tert*-Butyl 3-(6-(2-chlorophenoxy)pyridin-3-yl)azetidine-1-carboxylate

In analogy to the procedure described in example 48 a, 5-bromo-2-(2-chlorophenoxy)pyridine (CAS RN 1240670-82-9) was reacted with *tert*-butyl 3-bromoazetidine-1-carboxylate to give the title compound as yellow oil. MS (ESI): m/z = 361.2 $[M+H]^+$.

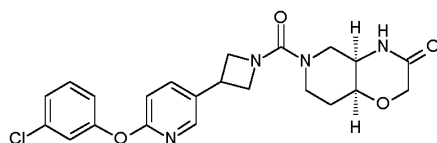
Step b) 5-(Azetidin-3-yl)-2-(2-chlorophenoxy)pyridine 4-methylbenzenesulfonate

In analogy to the procedure described in example 48 b, *tert*-butyl 3-(6-(2-chlorophenoxy)pyridin-3-yl)azetidine-1-carboxylate was reacted with 4-methylbenzenesulfonic acid hydrate to obtain the title compound as white crystals. MS (ESI): m/z = 261.1 $[M+H]^+$.

Example 53

(4aR,8aS)-6-(3-(6-(3-Chlorophenoxy)pyridin-3-yl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one

- 87 -



In analogy to the procedure described in example 48, (4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (2S,3S)-2,3-bis((4-methylbenzoyl)oxy)succinate was reacted with 5-(azetidin-3-yl)-2-(3-chlorophenoxy)pyridine 4-methylbenzenesulfonate to obtain the title compound as off-white solid. MS (ESI): $m/z = 443.3 [M+H]^+$.

Step a) *tert*-Butyl 3-(6-(3-chlorophenoxy)pyridin-3-yl)azetidine-1-carboxylate

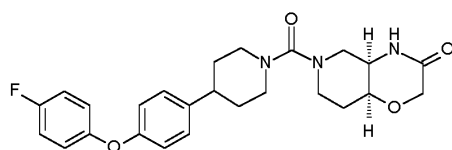
In analogy to the procedure described in example 48 a, 5-bromo-2-(3-chlorophenoxy)pyridine (CAS RN 1240670-82-9) was reacted with *tert*-butyl 3-bromoazetidine-1-carboxylate to give the title compound as off-white solid. MS (ESI): $m/z = 361.2 [M+H]^+$.

Step b) 5-(Azetidin-3-yl)-2-(3-chlorophenoxy)pyridine 4-methylbenzenesulfonate

In analogy to the procedure described in example 48 b, *tert*-butyl 3-(6-(3-chlorophenoxy)pyridin-3-yl)azetidine-1-carboxylate was reacted with 4-methylbenzenesulfonic acid hydrate to obtain the title compound as white crystals. MS (ESI): $m/z = 261.2 [M+H]^+$.

Example 54

(4aR,8aS)-6-[4-[4-(4-Fluorophenoxy)phenyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



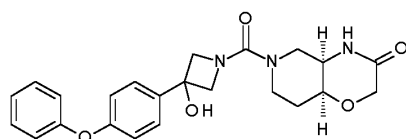
A mixture of (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (90.1 mg, 0.280 mmol, BB2a), DIPEA (362.1 mg, 2.8 mmol) and 4-[4-(4-fluorophenoxy)phenyl]piperidine; 2,2,2-trifluoroacetic acid (50 mg, 0.130 mmol, TFA salt of CAS RN 224449-70-1) in ACN (1 mL) was stirred at 80 °C for 12 h. The reaction mixture was brought to dryness under reduced pressure. The residue

- 88 -

was purified by prep. HPLC (0.225% TFA) and lyophilized to give the title compound (19.6 mg, 0.040 mmol, 32.5% yield) as yellow solid. MS (ESI): $m/z = 454.4$ $[M+H]^+$.

Example 55

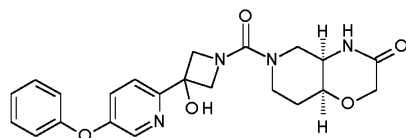
(4aR,8aS)-6-[3-Hydroxy-3-(4-phenoxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



In analogy to the procedure described in example 47, (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate was reacted with 3-(4-phenoxyphenyl)azetidin-3-ol; 2,2,2-trifluoroacetic acid (TFA salt of CAS RN 2229540-84-3) to give the title compound as white solid. MS (ESI): $m/z = 424.1$ $[M+H]^+$.

Example 56

(4aR,8aS)-6-[3-Hydroxy-3-(5-phenoxy-2-pyridyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

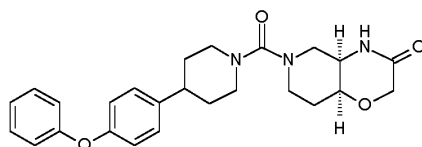


In analogy to the procedure described in example 47, (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate was reacted with 3-(5-phenoxy-2-pyridyl)azetidin-3-ol; 2,2,2-trifluoroacetic acid (TFA salt of CAS RN 2355937-31-2) to give the title compound as light yellow solid. MS (ESI): $m/z = 425.3$ $[M+H]^+$.

Example 57

(4aR,8aS)-6-[4-(4-Phenoxyphenyl)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

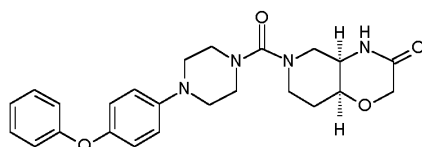
- 89 -



In analogy to the procedure described in example 47, (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate was reacted with 4-(4-phenoxyphenyl)piperidine; 2,2,2-trifluoroacetic acid (CAS RN 1247029-36-2) to give the title compound as white solid. MS (ESI): $m/z = 436.1$ $[M+H]^+$.

Example 58

(4aR,8aS)-6-[4-(4-Phenoxyphenyl)piperazine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



In analogy to the procedure described in example 47, (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate was reacted with 1-(4-phenoxyphenyl)piperazine; 2,2,2-trifluoroacetic acid (TFA salt of CAS RN 62755-61-7) to give the title compound as light red solid. MS (ESI): $m/z = 437.3$ $[M+H]^+$.

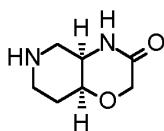
Synthesis of building blocks

BB1a & BB1b

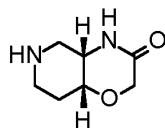
(+)-cis-4a,5,6,7,8,8a-Hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one

and

(-)-cis-4a,5,6,7,8,8a-Hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one



BB1a (+)



BB1b (-)

- 90 -

The enantiomers of rac-(4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one dihydrochloride (BB1, 500 mg, 2.18 mmol, ChemBridge Corporation) were separated by preparative chiral HPLC (ReprosilChiral NR column) using an isocratic mixture of EtOH (containing 0.05% of NH₄OAc) : n-heptane (30 : 70).

- 5 First eluting enantiomer: (+)-cis-4a,5,6,7,8,8a-Hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one (BB1a). Yellow solid (0.150 g; 44.0%). MS (ESI): m/z = 157.1 [M+H]⁺.

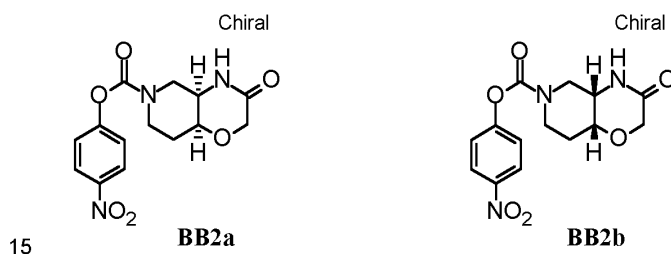
Second eluting enantiomer: (-)-cis-4a,5,6,7,8,8a-Hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one. (BB1b). Yellow solid (0.152 g; 44.6%). MS (ESI): m/z = 157.1 [M+H]⁺.

BB2a and BB2b

- 10 **4-Nitrophenyl (4aR,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (BB2a)**

and

4-nitrophenyl (4aS,8aR)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (BB2b)



To a suspension of rac-(4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one; dihydrochloride salt (4.5 g, 19.6 mmol, BB1) in dry DCM (125 mL) at 0 °C was added DIPEA (6.35 g, 8.58 mL, 49.1 mmol) followed by 4-nitrophenyl carbonochloridate (4.35 g, 21.6 mmol). The reaction mixture was stirred at 0 °C for 10 min and at RT for 2 hours.

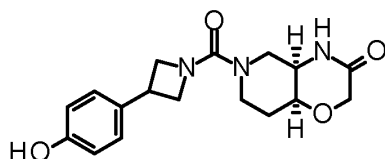
- 20 The crude reaction was diluted with DCM and transferred into a separating funnel for extraction with sat. aq. Na₂CO₃ solution. The organic phase was collected and the aqueous phase was back-extracted with DCM. The combined organic phases were dried over Na₂SO₄ and evaporated down to dryness to yield 6.62 g of a crude racemic product (BB7) as a yellow solid. The crude material was directly submitted for a chiral SFC separation to
- 25 yield enantiomer BB2b (2.72 g, second eluting enantiomer) as a yellow solid and

- 91 -

enantiomer BB2a (3.25 g, first eluting enantiomer) as a light beige solid but contaminated with BB2b. A further SFC chiral separation was carried out to yield 2.71 g of BB2a. MS (ESI): $m/z = 322.2$ $[M+H]^+$ for both enantiomers.

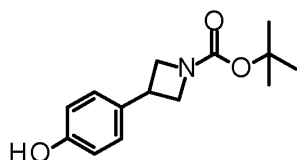
BB3

5 **(4aR,8aS)-6-[3-(4-Hydroxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one**



To a solution of (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (BB2a, 1.22 g, 3.8 mmol) and 4-(azetidin-3-yl)phenol
 10 trifluoroacetate salt (1 g, 3.8 mmol) in ACN (10 mL) was added DIPEA (4.91 g, 37.99 mmol) and the reaction mixture heated to 80°C for 12 hours. The solution was evaporated to dryness and the residue was taken up in ACN (20 mL). The resulting solid precipitate was filtered, washed with ACN and further dried to give the title compound (0.65 g, 51.6%) as off-white solid. MS (ESI): $m/z = 332.1$ $[M+H]^+$.

15 **Step a) *tert*-Butyl 3-(4-hydroxyphenyl)azetidine-1-carboxylate**

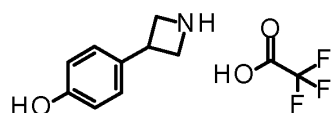


To a solution of 4-bromophenol (3.6 g, 21.18 mmol, CAS RN 106-41-2), *tert*-butyl 3-bromoazetidine-1-carboxylate (5 g, 21.18 mmol, CAS RN 1064194-10-0),
 Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (0.237 g, 0.210 mmol), NiCl₂-glyme (0.023 g, 0.110 mmol),
 20 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (0.034 g, 0.130 mmol), bis(trimethylsilyl)silyl-trimethyl-silane (5.26 g, 21.18 mmol) and Na₂CO₃ (4.49 g, 42.35 mmol) in DME (100 mL). The reaction mixture was stirred and irradiated with a 34 W blue LED lamp (7 cm away), with cooling fan to keep the reaction temperature at 25°C for 14 hours. The reaction was filtered, the filtrate evaporated and purified by preparative

- 92 -

HPLC to give the title compound (1.8 g, 34%) as light yellow solid. MS (ESI): $m/z = 194.0$ $[M+H]^+$.

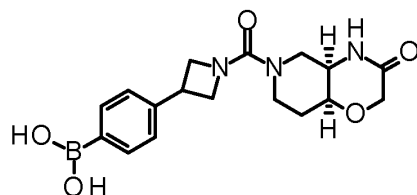
Step b) 4-(Azetidin-3-yl)phenol; trifluoroacetate salt



- 5 To a solution of *tert*-butyl 3-(4-hydroxyphenyl)azetidine-1-carboxylate (1 g, 4.01 mmol) in DCM (30 mL) was added TFA (5.0 mL) and the reaction mixture was stirred at room temperature for 12 hours. The mixture was evaporated *in vacuo* to give the crude title compound (1 g, 94.7% yield) as yellow oil. MS (ESI): $m/z = 150.1$ $[M+H]^+$.

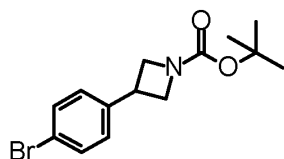
BB4

- 10 **[4-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]phenyl]boronic acid**



- To a solution of (4aR,8aS)-6-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (0.2 g, 0.453 mmol) in H₂O (1.2 mL) and acetone (2.4 mL) was added NaIO₄ (0.29 g, 1.36 mmol) and NH₄OAc (0.21 g, 2.72 mmol) at room temperature. Then, the reaction mixture was stirred at 30 °C for 16 hours. The mixture was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude title compound (0.176 g) as white solid. MS (ESI): $m/z = 360.2$ $[M+H]^+$.
- 20 Step a) *tert*-Butyl 3-(4-bromophenyl)azetidine-1-carboxylate

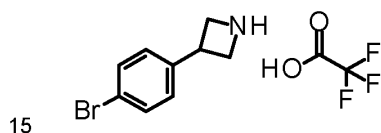
- 93 -



To a solution of *tert*-butyl 3-iodoazetidine-1-carboxylate (3.0 g, 10.6 mmol, CAS RN 254454-54-1) in 2-propanol (30 mL) was added a solution of 4-bromophenylboronic acid (4.26 g, 21.19 mmol, CAS RN 5467-74-3) in 2-propanol (15 mL) at room temperature.

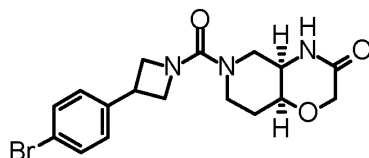
- 5 Then, rac-(1R,2R)-2-aminocyclohexan-1-ol (73.18 mg, 0.640 mmol), a 1M solution of sodium bis(trimethylsilyl)amide in THF (21.19 mL, 21.19 mmol) and nickel(II) iodide (198.69 mg, 0.640 mmol) were added to the mixture which was stirred at room temperature for 30 min. The mixture was transferred into 10 sealed tubes and heated under microwave irradiation at 80 °C for 30 min. The mixtures were combined, diluted with
- 10 water (100 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was then purified by MPLC to yield the title compound (2.8 g, 84.6%) as yellow oil. MS (ESI): m/z = 256.0 [M+H]⁺.

Step b) 3-(4-Bromophenyl)azetidine; trifluoroacetate salt



To a solution of *tert*-butyl 3-(4-bromophenyl)azetidine-1-carboxylate (2.7 g, 8.65 mmol) in DCM (50 mL) was added TFA (8.0 mL) and the reaction mixture was stirred at room temperature for 12 hours. The mixture was evaporated to dryness to give the crude title compound (2.8 g, 99.3%) as yellow oil. MS (ESI): m/z = 214.0 [M+H]⁺.

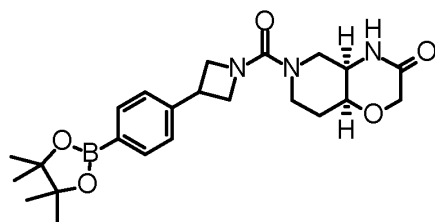
- 20 Step c) (4aR,8aS)-6-[3-(4-Bromophenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



- 94 -

To a solution of (4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (BB2a, 2.36 g, 7.36 mmol) and 3-(4-bromophenyl)azetidine trifluoroacetate salt (2 g, 6.13 mmol) in ACN (20 mL) was added DIPEA (7.92 g, 61.33 mmol) and the reaction mixture heated to 80°C for 12 hours. The mixture was evaporated to dryness and the residue purified by preparative HPLC to give the title compound (1.1 g, 45.5%) as yellow gum. MS (ESI): $m/z = 396.1 [M+2+H]^+$.

Step d) (4aR,8aS)-6-(3-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one



In a sealed tube, bis(pinacolato)diboron (0.97 g, 3.8 mmol), KOAc (0.747 g, 7.61 mmol) and (4aR,8aS)-6-[3-(4-bromophenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (1 g, 2.54 mmol) were mixed in dioxane (20 mL). Then, $PdCl_2(dppf) \cdot CH_2Cl_2$ (0.207 g, 0.250 mmol) was added, the reaction mixture purged with N_2 and heated to 90°C for 12 hours. The mixture was filtered, the filtrate evaporated and the residue purified by preparative HPLC to yield the title compound (0.65 g, 58%) as a 3/2 mixture of boronic acid/boronic ester as light brown solid. MS (ESI): $m/z = 442.1 [M+H]^+$.

Example 59

A compound of formula (I) can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	<u>Per tablet</u>
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg

- 95 -

Hydroxypropylmethylcellulose	<u>20 mg</u>
	425 mg

Example 60

A compound of formula (I) can be used in a manner known per se as the active ingredient
5 for the production of capsules of the following composition:

	<u>Per capsule</u>
Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
10 Talc	4.5 mg
Magnesium stearate	<u>0.5 mg</u>
	220.0 mg