

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 or
5 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 brain, the main
15 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 microglia cells (Chanda, P.K., *et al.*, *Molecular
20 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-oxygenase which produces PGs and the 5-lipoxygenase which produces LTs. Of the
25 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 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 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, 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 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-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.).

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 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

- 3 -

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 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
5 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 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
10 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, 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
15 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 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
20 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.).

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-
25 tumorigenic actions, including anti-proliferation, apoptosis induction and anti-metastatic effects. MAGL as an important decomposing enzyme for 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* **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).
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The endocannabinoid system is also involved in many gastrointestinal physiological and physiopathological actions (Marquez L. *et al.*, *PLoS One* **2009**, 4(9), e6893). All these effects

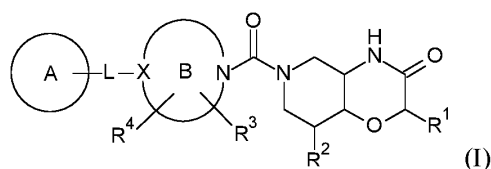
- 4 -

are driven 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 K. *et al.*, *Gastroenterology* **2005**, 129(2), 437-453; Duncan, M. *et al.*, *Aliment Pharmacol Ther* **2005**, 22(8), 667-683). Activation of CB1 produces anti-emetic, anti-motility, and anti-inflammatory effect, and help to modulate pain (Perisetti, A. *et al.*, *Ann Gastroenterol* **2020**, 33(2), 134-144). CB2 receptors are expressed in immune cells such as plasma cells and macrophages, in the lamina propria of the GI tract (Wright K. *et al.*, *Gastroenterology* **2005**, 129(2), 437-453), 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 colonic tissue in UC patients (Marquez L. *et al.*, *PLoS One* **2009**, 4(9), e6893) and 2-AG levels are increased in plasma of IBD patients (Grill, M. *et al.*, *Sci Rep* **2019**, 9(1), 2358). 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 L. *et al.*, *PLoS One* **2009**, 4(9), e6893). Furthermore, MAGL inhibition improves gut wall integrity and intestinal permeability via a CB1 driven MoA (Wang, J. *et al.*, *Biochem Biophys Res Commun* **2020**, 525(4), 962-967).

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, 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

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

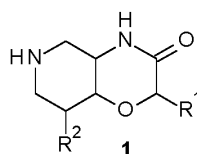


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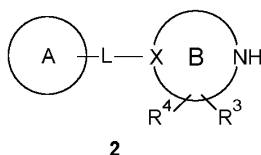
or a pharmaceutically acceptable salt thereof, wherein A, B, L, X, and R¹ to R⁴ are as described herein.

In one aspect, the present invention provides a process of manufacturing the urea compounds of formula (I) described herein, and pharmaceutically acceptable salts thereof, comprising:

- 5 (a) reacting a first amine of formula **1**, wherein R¹ and R² are as described herein, preferably wherein R¹ and R² are hydrogen,



with a secondary amine **2**, wherein A, B, L, X, R³ and R⁴ are as described herein



- 10 in the presence of a base and a urea forming reagent, to form said compound of formula (I); and optionally
- (b) transforming said compound of formula (I) to a pharmaceutically acceptable salts thereof.

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

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

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

- 20 In a further aspect, the present invention provides the use of a compound of formula (I) as described herein or of a pharmaceutical composition described herein for inhibiting monoacylglycerol lipase (MAGL) in a mammal.

In a further aspect, the present invention provides the use of a compound of formula (I) as described herein or of a pharmaceutical composition described herein for the treatment or

- 6 -

prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.

In a further aspect, the present invention provides the use of a compound of formula (I) as described herein or of a pharmaceutical composition described herein for the treatment or
5 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 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.

10 **Detailed Description of the Invention**

Definitions

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
15 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 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,
20 of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

The term "alkyl" refers to a mono- or multivalent, e.g., a mono- or bivalent, linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms ("C₁-C₆-alkyl"), e.g., 1, 2, 3, 4, 5, or 6
25 carbon atoms. In some 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. A particularly preferred, yet non-limiting example of alkyl is methyl.

The term "alkoxy" refers to an alkyl group, as previously defined, attached to the parent
30 molecular moiety via an oxygen atom. Unless otherwise specified, the alkoxy group contains 1 to 6 carbon atoms ("C₁-C₆-alkoxy"). In some preferred embodiments, the alkoxy group contains

- 7 -

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.

- 5 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 “bridged bicyclic heterocycle” refers to a chemical entity consisting of two
10 heterocyclyl moieties as defined herein, or to a combination of one heterocyclyl and one cycloalkyl moiety, having two ring 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. In some embodiments, the bridged bicyclic heterocycle is a 6-14 membered bridged bicyclic heterocycle comprising 1-3 heteroatoms selected from N, S, and O. In some preferred embodiments, the bridged bicyclic
15 heterocycle is a 6-9 membered bridged bicyclic heterocycle comprising 1-2 heteroatoms selected from N and O. In some particularly preferred embodiments, the bridged bicyclic heterocycle is a 6-8 membered bridged bicyclic heterocycle comprising 1 nitrogen atom. Some preferred, yet non-limiting examples of bridged bicyclic heterocycles include 8-azabicyclo[3.2.1]octane-yl; 3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrolyl; 3-azabicyclo[3.1.0]hexanyl; 2-
20 azabicyclo[2.2.1]heptane-yl; 3-azabicyclo[3.2.1]octane-yl; 2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrolyl; 3-oxa-9-azabicyclo[3.3.1]nonane-yl; and 3-azabicyclo[3.1.1]heptane-yl.

- The term “heterocyclyl” refers to a saturated or partly unsaturated monocyclic ring system of 3 to 10 ring atoms, preferably 3 to 8 ring atoms, wherein 1, 2, or 3 of said ring atoms are heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Preferably, 1 to 2
25 of said ring atoms are selected from N and O, the remaining ring atoms being carbon. Some non-limiting examples of heterocyclyl groups include azetidin-3-yl, azetidin-2-yl, oxetan-3-yl, oxetan-2-yl, 2-oxopyrrolidin-1-yl, 2-oxopyrrolidin-3-yl, 5-oxopyrrolidin-2-yl, 5-oxopyrrolidin-3-yl, 2-oxo-1-piperidyl, 2-oxo-3-piperidyl, 2-oxo-4-piperidyl, 6-oxo-2-piperidyl, 6-oxo-3-piperidyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, morpholino, morpholin-2-yl
30 and morpholin-3-yl.

The term “cycloalkyl” as used herein refers to a saturated or partly unsaturated monocyclic hydrocarbon group of 3 to 10 ring carbon atoms (“C₃-C₁₀-cycloalkyl”). In some preferred

- 8 -

embodiments, the cycloalkyl group is a saturated monocyclic hydrocarbon group of 3 to 8 ring carbon atoms. 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

5 particularly preferred, yet non-limiting example of cycloalkyl is cyclopropyl.

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. A particularly preferred, yet non-limiting example of aryl is phenyl.

10 The term "heteroaryl" refers to a mono- or multivalent, monocyclic or bicyclic, 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. Preferably, "heteroaryl" refers to a 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected
15 from O, S and N. Most preferably, "heteroaryl" refers to a 5-10 membered heteroaryl comprising 1 to 2 heteroatoms independently selected from O and N. Some non-limiting examples of heteroaryl include 2-pyridyl, 3-pyridyl, 4-pyridyl, 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, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, 5,6,7,8-tetrahydroisoquinolin-1-yl, 5,6,7,8-tetrahydroisoquinolin-3-yl, 5,6,7,8-tetrahydroisoquinolin-4-yl, 5,6,7,8-tetrahydroisoquinolin-5-yl, 5,6,7,8-tetrahydroisoquinolin-6-yl, 5,6,7,8-tetrahydroisoquinolin-7-yl, and 5,6,7,8-tetrahydroisoquinolin-8-yl. Particularly preferred, yet non-limiting examples of heteroaryl are 2-pyridyl, 1H-pyrazol-3-yl, and 5,6,7,8-tetrahydroisoquinolin-3-yl.
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The term "hydroxy" refers to an -OH group.

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

The term "alkylsulfonyl" refers to an alkyl group attached to the parent molecular moiety via an SO₂ moiety. A particularly preferred, yet non-limiting example of alkylsulfonyl is
30 methylsulfonyl.

- 9 -

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. A particularly preferred, yet non-limiting example of
5 haloalkyl is trifluoromethyl (CF₃).

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-
10 limiting example of haloalkoxy is trifluoromethoxy (-OCF₃).

The term "pharmaceutically acceptable salt" refers to those salts which retain the 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
15 hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric 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
20 an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts 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,
25 lysine, arginine, N-ethylpiperidine, piperidine, polyimine resins and the like. Particular pharmaceutically 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.
30 Protective groups can be removed at the appropriate point. Exemplary protective groups are amino-protective groups, carboxy-protective groups or hydroxy-protective groups. Particular protective groups are the tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz),

- 10 -

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-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.

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 urea forming reagents include bis(trichloromethyl) carbonate, phosgene, trichloromethyl chloroformate, (4-nitrophenyl)carbonate 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, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. In a preferred embodiment, the compound of formula (I) according to the invention is a *cis*-enantiomer of formula (Ia) or (Ib), respectively, as described herein.

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 "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 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 clinical symptoms of the state, disorder or condition developing in a mammal and especially a

- 11 -

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 the nervous tissue, which is the main tissue component of the two parts of the nervous 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 central nervous system immediately, e.g., as a result of traumatic brain injury (TBI).

10 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 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 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 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.

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

- 12 -

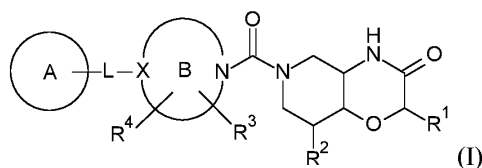
not limited to, neurotoxicity resulting from exposure to substances used in chemotherapy, radiation treatment, drug therapies, drug abuse, and organ transplants, as well as exposure to heavy metals, certain foods and food additives, pesticides, industrial and/or cleaning solvents, cosmetics, and some naturally occurring substances.

- 5 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 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, bovinos, equines, and porcines. In a particularly preferred embodiment, the term “mammal” refers to humans.

Compounds of the Invention

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



- 15 or pharmaceutically acceptable salts thereof, wherein:

X is N or C-R⁵;

L is selected from a covalent bond, $-(CH_2)_n-O-$, $-O-(CH_2)_p-$, and $-SO_2-$;

n is an integer selected from 0, 1, 2 and 3;

p is an integer selected from 1, 2 and 3;

- 20 A is:

(i) C₆₋₁₄-aryl substituted with R⁶, R⁷ and R⁸; or

(ii) 5-14 membered heteroaryl substituted with R⁹, R¹⁰ and R¹¹; or

B is a bridged bicyclic heterocycle;

R¹ is hydrogen or C₁₋₆-alkyl;

- 25 R² is hydrogen or C₁₋₆-alkyl;

R³ is hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen or hydroxy;

R⁴ is hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen or hydroxy;

R⁵ is hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen or hydroxy; and

- 13 -

R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} are independently selected from hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, SF₅, C₁₋₆-alkylsulfonyl, cyano, C₃₋₁₀-cycloalkyl, C₆₋₁₄-aryl, and 5-14 membered heteroaryl, wherein said C₃₋₁₀-cycloalkyl, C₆₋₁₄-aryl, and 5-14 membered heteroaryl are optionally substituted with 1-2 substituents selected from halogen, cyano, SF₅, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, and halo-C₁₋₆-alkoxy.

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

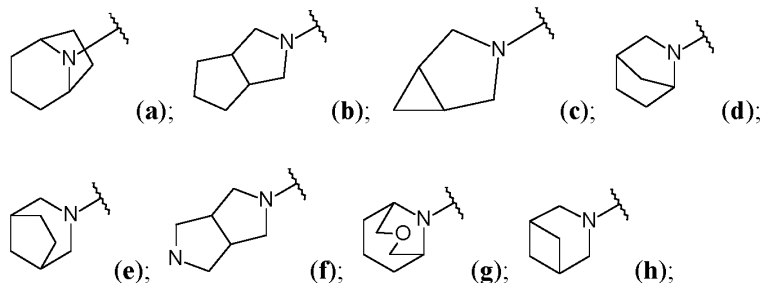
- E1. The compound of formula (I) according to A1, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.
- E2. The compound of formula (I) according to A1 or E1, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.
- E3. The compound of formula (I) according to any one of A1 and E1 to E2, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.
- E4. The compound of formula (I) according to any one of A1 and E1 to E3, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.
- E5. The compound of formula (I) according to any one of A1 and E1 to E4 or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.
- E6. The compound of formula (I) according to any one of A1 and E1 to E5, or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, and halogen.
- E7. The compound of formula (I) according to any one of A1 and E1 to E5, or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from halo-C₁₋₆-alkyl and halogen.
- E8. The compound of formula (I) according to any one of A1 and E1 to E5, or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from CF₃, chloro, and fluoro.

- 14 -

- E9. The compound of formula (I) according to any one of A1 and E1 to E8, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from hydrogen and halogen.
- E10. The compound of formula (I) according to any one of A1 and E1 to E8, or a pharmaceutically acceptable salt thereof, wherein R^7 is halogen.
- E11. The compound of formula (I) according to any one of A1 and E1 to E8, or a pharmaceutically acceptable salt thereof, wherein R^7 is fluoro or chloro.
- E12. The compound of formula (I) according to any one of A1 and E1 to E8, or a pharmaceutically acceptable salt thereof, wherein R^7 is fluoro.
- E13. The compound of formula (I) according to any one of A1 and E1 to E12, or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen.
- E14. The compound of formula (I) according to any one of A1 and E1 to E13, or a pharmaceutically acceptable salt thereof, wherein R^9 is selected from hydrogen, C_{3-10} -cycloalkyl, and C_{6-14} -aryl, wherein said C_{6-14} -aryl is substituted with 1-2 substituents selected from halogen and halo- C_{1-6} -alkyl.
- E15. The compound of formula (I) according to any one of A1 and E1 to E14, or a pharmaceutically acceptable salt thereof, wherein R^{10} is selected from hydrogen and halogen.
- E16. The compound of formula (I) according to any one of A1 and E1 to E15, or a pharmaceutically acceptable salt thereof, wherein R^{11} is hydrogen.
- E17. The compound of formula (I) according to any one of A1 and E1 to E16, or a pharmaceutically acceptable salt thereof, wherein X is $C-R^5$.
- E18. The compound of formula (I) according to any one of A1 and E1 to E17, or a pharmaceutically acceptable salt thereof, wherein L is selected from $-(CH_2)_n-O-$ and $-O-(CH_2)_p-$.
- E19. The compound of formula (I) according to any one of A1 and E1 to E18, or a pharmaceutically acceptable salt thereof, wherein n is an integer selected from 0 and 1.

- 15 -

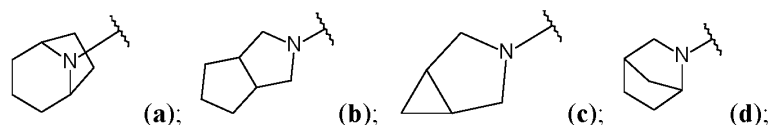
- E20. The compound of formula (I) according to any one of A1 and E1 to E19, or a pharmaceutically acceptable salt thereof, wherein p is 1.
- E21. The compound of formula (I) according to any one of A1 and E1 to E20, or a pharmaceutically acceptable salt thereof, wherein A is C₆₋₁₄-aryl substituted with R⁶, R⁷ and R⁸.
- E22. The compound of formula (I) according to any one of A1 and E1 to E20, or a pharmaceutically acceptable salt thereof, wherein A is phenyl substituted with R⁶, R⁷ and R⁸.
- E23. The compound of formula (I) according to any one of A1 and E1 to E22, or a pharmaceutically acceptable salt thereof, wherein B is a 6-14 membered bridged bicyclic heterocycle comprising 1-3 heteroatoms selected from N, S, and O.
- E24. The compound of formula (I) according to any one of A1 and E1 to E22, or a pharmaceutically acceptable salt thereof, wherein B is a 6-9 membered bridged bicyclic heterocycle comprising 1-2 heteroatoms selected from N and O.
- E25. The compound of formula (I) according to any one of A1 and E1 to E22, or a pharmaceutically acceptable salt thereof, wherein B is a 6-8 membered bridged bicyclic heterocycle comprising 1 nitrogen atom.
- E26. The compound of formula (I) according to any one of A1 and E1 to E22, or a pharmaceutically acceptable salt thereof, wherein B is selected from 8-azabicyclo[3.2.1]octan-8-yl **(a)**; 3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl **(b)**; 3-azabicyclo[3.1.0]hexan-3-yl **(c)**; 2-azabicyclo[2.2.1]heptan-2-yl **(d)**; 3-azabicyclo[3.2.1]octan-3-yl **(e)**; 2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-yl **(f)**; 3-oxa-9-azabicyclo[3.3.1]nonan-9-yl **(g)**; and 3-azabicyclo[3.1.1]heptan-3-yl **(h)**:



- 16 -

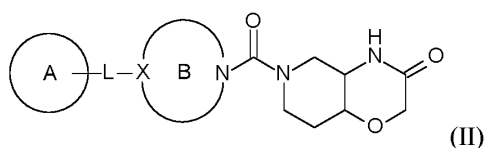
wherein a wavy line indicates the point of attachment to the carbonyl bridge bridging B to the hexahydropyrido oxazinone core of formula (I).

- E27. The compound of formula (I) according to any one of A1 and E1 to E22, or a pharmaceutically acceptable salt thereof, wherein B is selected from 8-azabicyclo[3.2.1]octan-8-yl **(a)**; 3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl **(b)**;
 5 3-azabicyclo[3.1.0]hexan-3-yl **(c)**; and 2-azabicyclo[2.2.1]heptan-2-yl **(d)**;



wherein a wavy line indicates the point of attachment to the carbonyl bridge bridging B to the hexahydropyrido oxazinone core of formula (I).

- 10 E28. The compound of formula (I) according to A1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (II):

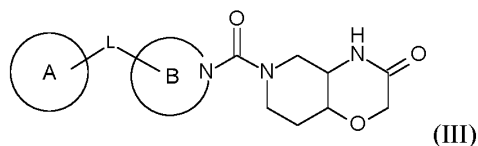


wherein:

- X is N or CH₃;
 L is selected from a covalent bond, $-(CH_2)_n-O-$, $-OCH_2-$, and $-SO_2-$;
 15 n is an integer selected from 0 and 1;
 A is:
 (i) C₆₋₁₄-aryl substituted with R⁶ and R⁷; or
 (ii) 5-14 membered heteroaryl substituted with R⁹ and R¹⁰; or
 20 B is a 6-9 membered bridged bicyclic heterocycle comprising 1-2 heteroatoms selected from N and O;
 R⁶ is selected from hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, and halogen;
 R⁷ is selected from hydrogen and halogen;
 R⁹ is selected from hydrogen, C₃₋₁₀-cycloalkyl, and C₆₋₁₄-aryl, wherein said C₆₋₁₄-aryl is
 25 substituted with 1-2 substituents selected from halogen and halo-C₁₋₆-alkyl; and
 R¹⁰ is selected from hydrogen and halogen.

- 17 -

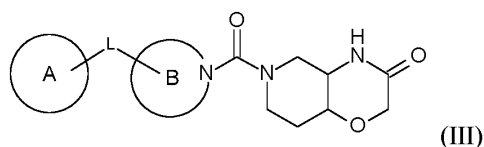
E29. The compound of formula (I) according to A1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (III):



wherein:

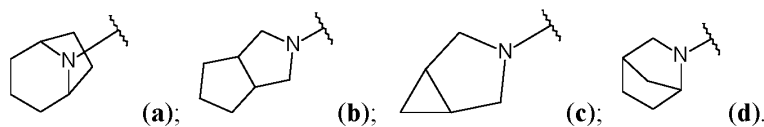
- 5 L is selected from $-(CH_2)_n-O-$ and $-OCH_2-$;
 n is an integer selected from 0 and 1;
 A is C_{6-14} -aryl substituted with R^6 and R^7 ;
 B is a 6-8 membered bridged bicyclic heterocycle comprising 1 nitrogen atom;
 R^6 is selected from halo- C_{1-6} -alkyl and halogen; and
 10 R^7 is halogen.

E30. The compound of formula (I) according to A1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (III):



wherein:

- 15 L is selected from $-(CH_2)_n-O-$ and $-OCH_2-$;
 n is an integer selected from 0 and 1;
 A is phenyl substituted with R^6 and R^7 ;
 B is selected from 8-azabicyclo[3.2.1]octan-8-yl (**(a)**); 3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl (**(b)**); 3-azabicyclo[3.1.0]hexan-3-yl (**(c)**); and 2-azabicyclo[2.2.1]heptan-2-yl (**(d)**):



wherein a wavy line indicates the point of attachment to the carbonyl bridge bridging B to the hexahydroindolizinone core of formula (I);

- R^6 is selected from CF_3 , chloro, and fluoro; and
 25 R^7 is fluoro or chloro.

- 18 -

- E31. The compound of formula (I) according to any one of A1 and E1 to E30, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is selected from the compounds disclosed in Table 1.
- E32. The compound of formula (I) according to any one of A1 and E1 to E30, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is selected from the group consisting of:
- (4aR,8aS)-6-[(1R,5S,6r)-6-[(2-chloro-4-fluoro-phenoxy)methyl]-3-azabicyclo[3.1.0]hexane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[5-(2-chloro-4-fluoro-phenoxy)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[rel-(1R,4R,5S)-5-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and
- (4aR,8aS)-6-[(1S,5R)-3-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-8-azabicyclo[3.2.1]octane-8-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one.
- E33. The compound of formula (I) according to any one of A1 and E1 to E30, or a pharmaceutically acceptable salt thereof, wherein R¹ and R² are both hydrogen.
- E34. The compound of formula (I) according to any one of A1 and E1 to E30, or a pharmaceutically acceptable salt thereof, wherein:
- X is N or CH;
- R³ and R⁴ are both hydrogen; and
- B is a 6-9 membered bridged bicyclic heterocycle comprising 1-2 heteroatoms selected from N and O.
- E35. The compound of formula (I) according to any one of A1 and E1 to E30, or a pharmaceutically acceptable salt thereof, wherein:
- X is CH;
- R³ and R⁴ are both hydrogen; and
- B is a 6-8 membered bridged bicyclic heterocycle comprising 1 nitrogen atom.

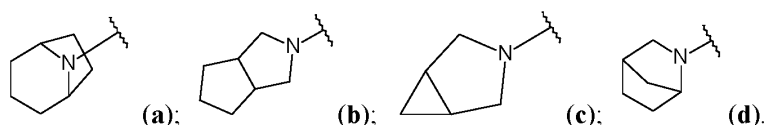
- 19 -

E36. The compound of formula (I) according to any one of A1 and E1 to E30, or a pharmaceutically acceptable salt thereof, wherein:

X is CH;

R³ and R⁴ are both hydrogen; and

- 5 B is selected from 8-azabicyclo[3.2.1]octan-8-yl (**(a)**); 3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl (**(b)**); 3-azabicyclo[3.1.0]hexan-3-yl (**(c)**); and 2-azabicyclo[2.2.1]heptan-2-yl (**(d)**):



10 wherein a wavy line indicates the point of attachment to the carbonyl bridge bridging B to the hexahydropyrido oxazinone core of formula (I).

E37. The compound of formula (I) according to any one of A1 and E1 to E30, or a pharmaceutically acceptable salt thereof, wherein:

L is selected from a covalent bond, $-(CH_2)_n-O-$, $-OCH_2-$, and $-SO_2-$;

n is an integer selected from 0 and 1;

15 A is:

(i) C₆₋₁₄-aryl substituted with R⁶ and R⁷; or

(ii) 5-14 membered heteroaryl substituted with R⁹ and R¹⁰;

R⁶ is selected from hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, and halogen;

R⁷ is selected from hydrogen and halogen;

20 R⁹ is selected from hydrogen, C₃₋₁₀-cycloalkyl, and C₆₋₁₄-aryl, wherein said C₆₋₁₄-aryl is substituted with 1-2 substituents selected from halogen and halo-C₁₋₆-alkyl; and

R¹⁰ is selected from hydrogen and halogen.

E38. The compound of formula (I) according to any one of A1 and E1 to E30, or a pharmaceutically acceptable salt thereof, wherein:

25 L is selected from $-(CH_2)_n-O-$ and $-OCH_2-$;

n is an integer selected from 0 and 1;

A is C₆₋₁₄-aryl substituted with R⁶ and R⁷;

R⁶ is selected from halo-C₁₋₆-alkyl and halogen; and

R⁷ is halogen.

- 20 -

E39. The compound of formula (I) according to any one of A1 and E1 to E30, or a pharmaceutically acceptable salt thereof, wherein:

- L is selected from $-(CH_2)_n-O-$ and $-OCH_2-$;
- n is an integer selected from 0 and 1;
- 5 A is phenyl substituted with R^6 and R^7 ;
- R^6 is selected from CF_3 , chloro, and fluoro; and
- R^7 is fluoro or chloro.

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 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 limited to, 2H , 3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , 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., ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means 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.

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

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
5 resulting products are known to those persons skilled in the art. The 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
10 more reaction steps, appropriate protective groups (as described e.g., in "Protective Groups in Organic Chemistry" by T. W. Greene and P. G. M. Wuts, 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.

15 If starting materials or intermediates contain stereogenic centers, compounds of formula (I) 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
20 using either a chiral adsorbent or a chiral eluent. It is equally 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
25 diastereomerically/enantiomerically enriched compounds of formula (I).

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 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
30 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).

- 22 -

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
- 5 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
- 10 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
- 15 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.
- 20 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.

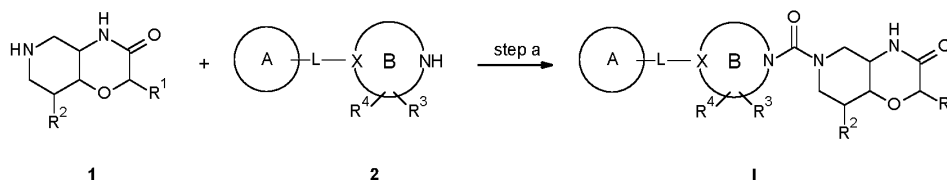
The following abbreviations are used in the present text:

- AcOH = acetic acid, ACN = acetonitrile, Bn = benzyl, Boc = tert-butyloxycarbonyl, CAS RN =
- 25 chemical abstracts registration number, Cbz = benzyloxycarbonyl, Cs₂CO₃ = cesium 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, DCM = dichloromethane, DEA = diethyl amine, DEAD = diethyl azodicarboxylate, DIAD = diisopropyl azodicarboxylate, DMAP = 4-dimethylaminopyridine, DME = dimethoxyethane,
- 30 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 =

- 23 -

electrospray ionization, EtOAc = ethyl acetate, EtOH = ethanol, h = hour(s), FA = formic acid, H₂O = water, H₂SO₄ = sulfuric acid, HATU = 1-[bis(dimethylamino)methylene]-1H-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 = 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, MgSO₄ = magnesium sulfate, min = minute(s), mL = milliliter, MPLC = medium pressure liquid chromatography, MS = mass spectrum, nBuLi = n-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-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 = 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 = tetrabutyl ammonium iodine, TEA = triethylamine, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMEDA = N,N,N',N'-tetramethylethylenediamine, ZnCl₂ = zinc chloride, Hal = halogen.

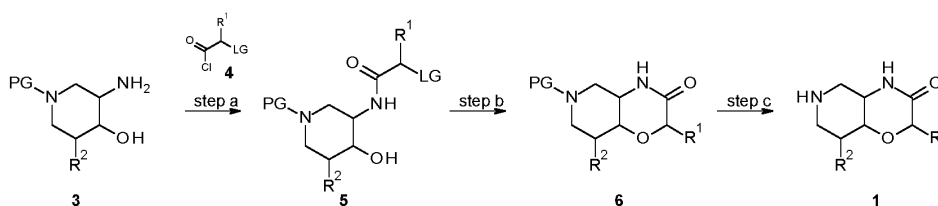
Compounds of formula **I** wherein A, L, X, R¹, R², R³ and R⁴ are as described herein can be synthesized in analogy to literature procedures and/or as depicted for example in Scheme 1.



Scheme 1

Accordingly, 4a,5,6,7,8,8a-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, 1,1'-carbonyldiimidazole or 1,1'-carbonyl-di-(1,2,4-triazole). 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.

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

Scheme 2

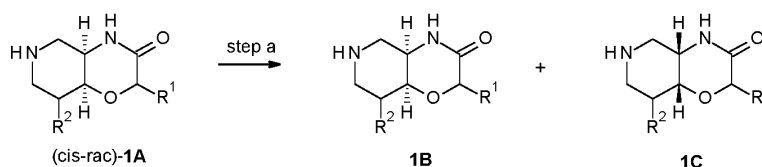
Thus, 3-aminopiperidin-4-ol derivatives **3** in which “PG” signifies a suitable protective group such as a Cbz or Boc protective group, and R^2 is as defined herein can be acylated for example with acyl chlorides **4** in which R^1 is as defined herein and “LG” signifies a suitable leaving group (e.g., 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 ($R^1 = H$) racemic (R^1 not H) or enantiomerically pure form (R^1 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).

- 25 -

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** and acid chlorides **4** (when R¹ is not H) are employed in their syntheses. In case racemization occurs at a stereocentre bearing R¹ during the conversion of **3** to **5** (step a) and/or of **5** to **6** (step b), the resulting diastereoisomers may be separated by chromatography (e.g. HPLC, chiral HPLC) or other methods known in the art. 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-(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).



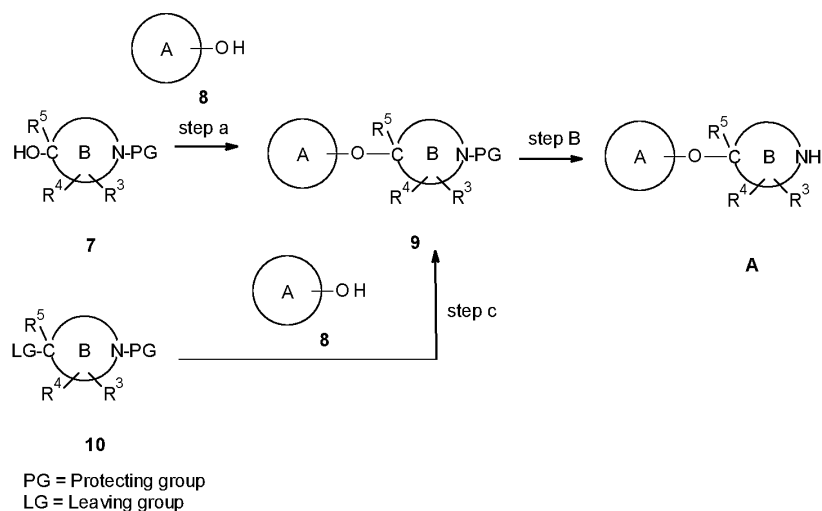
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Scheme 3

In some embodiments, intermediates **2** are intermediates of type **A**. Intermediates of type **A** in which A, B, R³ and R⁴ are as described herein and R⁵ is hydrogen, C₁₋₆-alkyl or halo-C₁₋₆-alkyl, 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.

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- 26 -

**Scheme 4**

Bicyclic compounds **7** in which PG signifies a suitable protective group such as a Boc, Cbz or Bn protecting group (either commercially available or prepared as described in literature, e.g. in *Eur. J. Org. Chem.* **2017**, 36, 5316; *Topics in Het. Chem.* **2014**, 35, 189; *World Journal of Pharmacy and Pharmaceutical Sciences* **2014**, 3(12), 536; *Chem. Rev.* **2014**, 114(16), 8257-8322) can be subjected to a Mitsunobu reaction with alcohol derivatives **8** using an appropriate phosphine such as triphenylphosphine and a dialkyl azodicarboxylate such as DEAD or DIAD in a suitable solvent such as THF to give intermediates **9** (step a). Mitsunobu reactions of that type are broadly described in literature (e.g. *Org. Chem. Front.* **2015**, 2, 739; *Chem. Rev.* **2009**, 109(6), 2551).

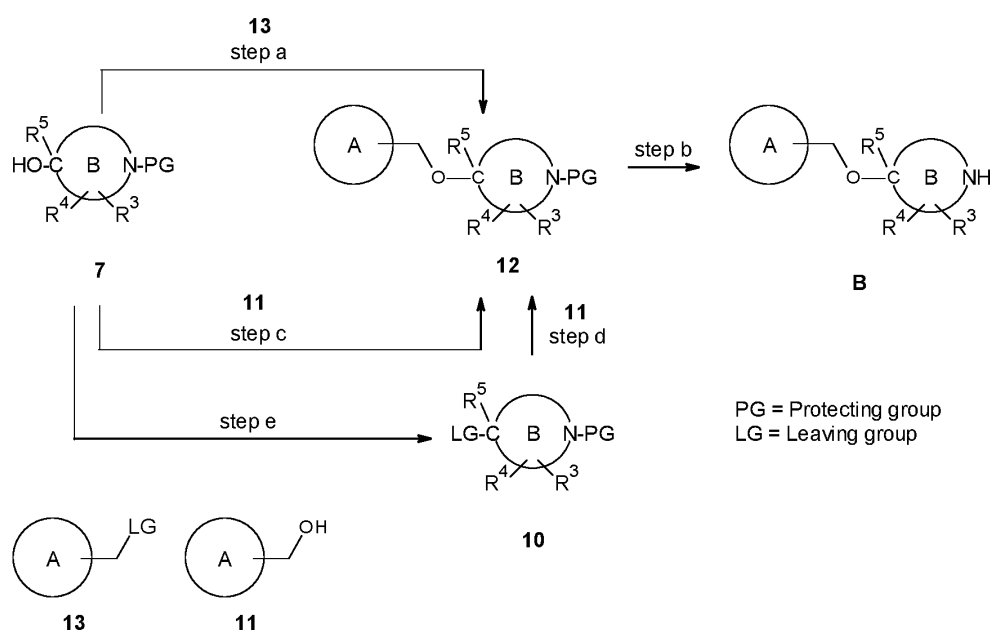
Removal of the protective group from intermediates **9**, applying methods known in the art, e.g., a Boc group using TFA in DCM or 4M HCl in dioxane at temperatures between 0°C and room temperature, a Bn or Cbz group using hydrogen in the presence of a suitable catalyst such as Pd or Pd(OH)₂ on charcoal 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 **A** (step b).

Intermediates **9** may alternatively be prepared by alkylation of compounds **8** with spirocyclic derivatives **10** (either commercially available or prepared by methods known in the art) in which LG signifies a suitable leaving group such as chlorine, bromine, iodine, OSO₂alkyl (e.g. mesylate (methanesulfonate), OSO₂fluoroalkyl (e.g. triflate (trifluoromethanesulfonate) or

- 27 -

OSO₂aryl (e.g. tosylate (p-toluenesulfonate) using a suitable base and an appropriate solvent (e.g. sodium hydride in DMF or potassium tert-butoxide in THF) at temperatures between 0°C and the boiling temperature of the solvent (step c).

In some embodiments, intermediates **2** are intermediates of type **B**. Intermediates of type **B** in which A, B, R³ and R⁴ are as described herein and R⁵ is hydrogen; C₁₋₆-alkyl or halo-C₁₋₆-alkyl can be prepared by methods well known in the art and as exemplified by the general synthetic procedures outlined in Scheme 5.

Scheme 5

- 10 Bicyclic compounds **7** in which PG is a suitable protective group can be alkylated with compounds **13** in which LG is a suitable leaving group such as chlorine, bromine, iodine, methanesulfonate, trifluoromethanesulfonate or p-toluenesulfonate (prepared by literature methods for example from compounds **11**) using using a suitable base and an appropriate solvent (e.g. sodium hydride in DMF or potassium tert-butoxide in THF) at temperatures between 0°C and the boiling temperature of the solvent (step c) to provide intermediates **12** (step a).
- 15

Removal of the protective group from intermediates **12**, applying methods known in the art and for example described under Scheme 4, step b, furnishes intermediates **B** (step b).

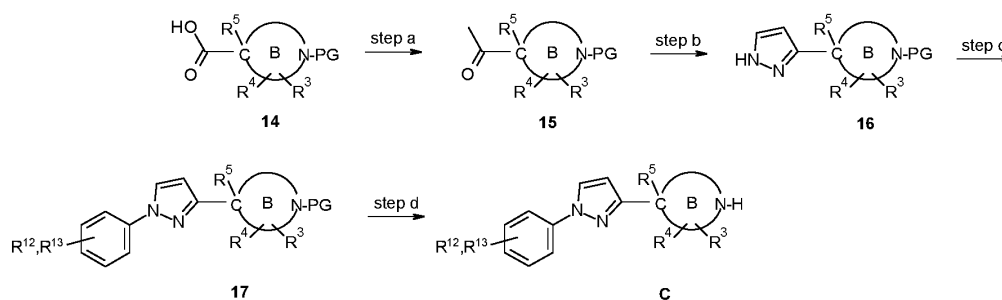
- 28 -

Alternatively, intermediates **12** may be prepared from intermediates **7** and compounds **11** via Mitsunobu reaction, applying for example the conditions described under Scheme 4, step a (step c).

Furthermore, intermediates **12** may be also prepared by alkylation of compounds **7** with compounds **10** and using for example the conditions described under Scheme 4, step c (step d).

Intermediates **10** in turn may be synthesized from compounds **7** converting the hydroxy function into a suitable leaving group such as an alkyl halide (e.g. bromine by using of PBr_3 , chlorine through the use of SOCl_2) or alkyl- or aryl-sulfonate such as methanesulfonate (using mesyl chloride) or p-toluenesulfonate (using tosyl chloride). Reactions of that type are broadly described in literature and are well known in the art.

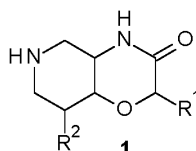
In some embodiments, intermediates **2** are intermediates of type **C**. Intermediates of type **C** in which A is aryl, B, R^3 and R^4 , R^{12} , R^{13} are as described herein and R^5 is hydrogen; C_{1-6} -alkyl or halo- C_{1-6} -alkyl can be prepared by methods well known in the art and as exemplified by the general synthetic procedures outlined in Scheme 6 and described in more detail in J. Med. Chem. 2018, 61, 3008-3026.



Scheme 6

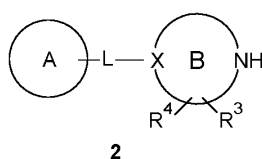
In one aspect, the present invention provides a process of manufacturing the urea compounds of formula (I) described herein, and pharmaceutically acceptable salts thereof, comprising:

- (a) reacting a first amine of formula **1**, wherein R^1 and R^2 are as described herein, preferably wherein R^1 and R^2 are hydrogen,



with a second amine **2**, wherein A, B, L, X, R^3 and R^4 are as described herein

- 29 -



in the presence of a base and a urea forming reagent, to form said compound of formula (I); and optionally

- (b) transforming said compound of formula (I) to a pharmaceutically acceptable salts thereof.

5

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, trichloromethyl chloroformate, (4-nitrophenyl)carbonate and 1,1'-carbonyldiimidazole, preferably wherein said

10

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

- 15 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.

- 20 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 formula (I) as described herein to the mammal.

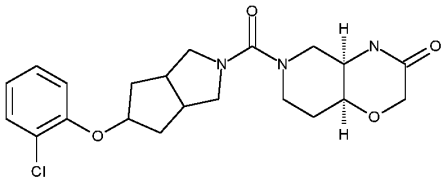
- 25 Compounds were profiled for MAGL inhibitory activity by determining the enzymatic activity by following the hydrolysis of the natural substrate 2-arachidonoylglycerol resulting in

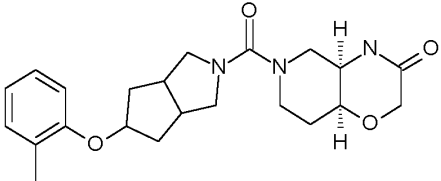
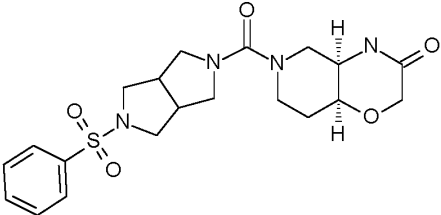
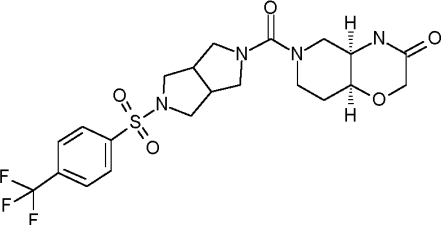
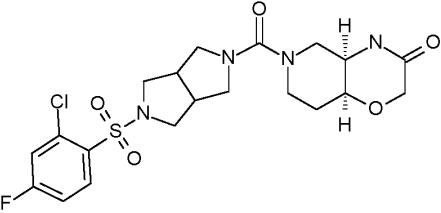
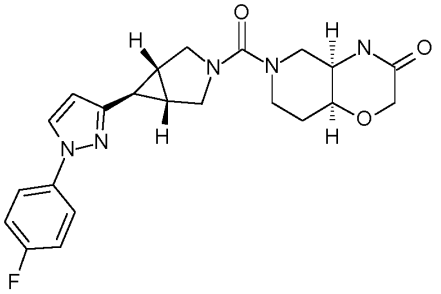
- 30 -

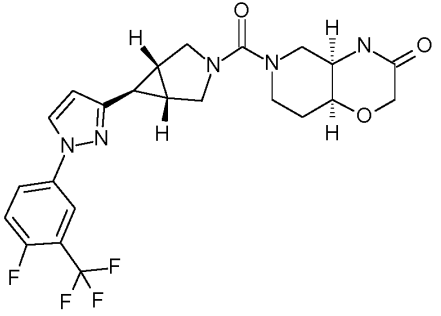
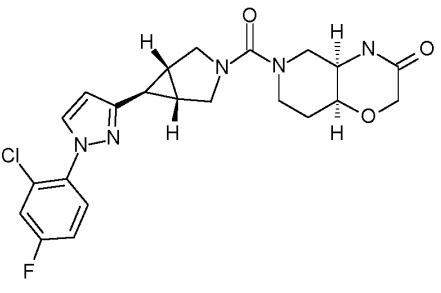
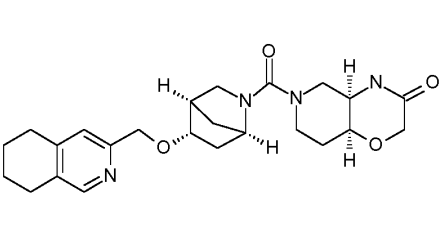
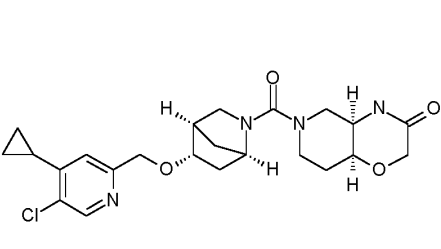
arachidonic acid, which can be followed by mass spectrometry. This assay is hereinafter abbreviated “2-AG assay”.

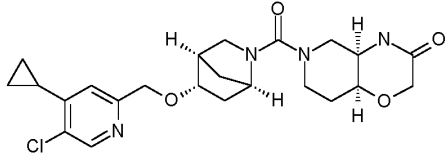
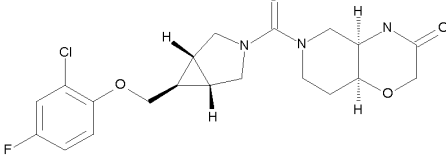
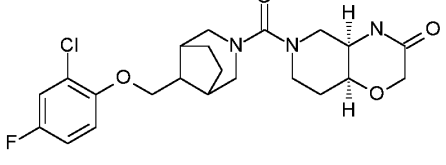
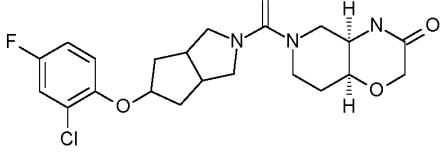
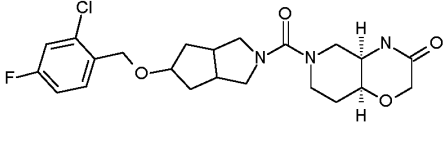
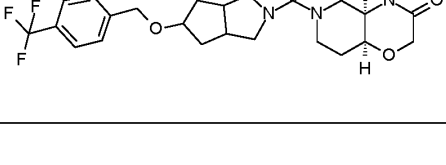
The 2-AG assay was carried out in 384 well assay plates (PP, Greiner Cat# 784201) in a total volume of 20 μ L. Compound dilutions were made in 100% DMSO (VWR Chemicals 23500.297) in a polypropylene plate in 3-fold dilution steps to give a final concentration range in the assay from 12.5 μ M to 0.8 pM. 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 EDTA (Fluka, 03690-100ml), 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 acetonitrile containing 4 μ M of d8-arachidonic acid. The 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 acetonitrile/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 calculated based on the ratio of intensities [arachidonic acid / d8-arachidonic acid].

Table 1

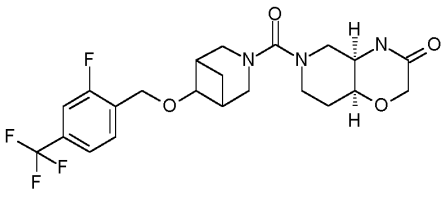
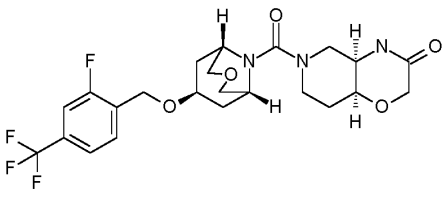
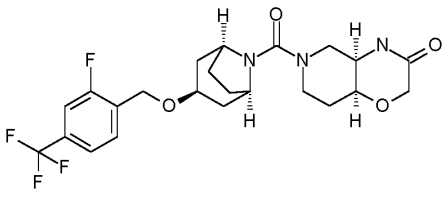
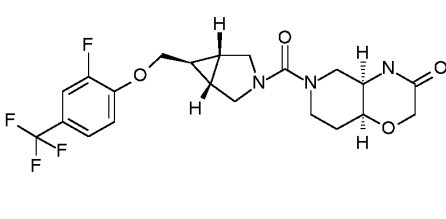
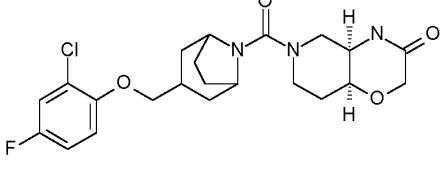
Ex.	Structure	IUPAC Name	MAGL IC50 (nM)
1		(4aR,8aS)-6-(5-(2-chlorophenoxy)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-carbonyl)-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	8.9

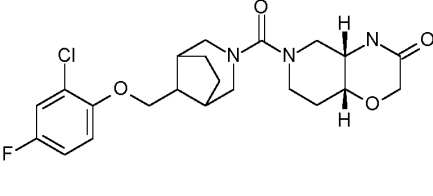
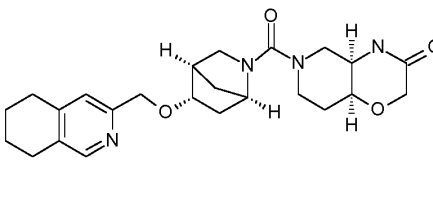
2		(4aR,8aS)-6-(5-(2-methylphenoxy)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-carbonyl)-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	19.8
3		(4aR,8aS)-6-(5-(benzenesulfonyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	2278.6
4		(4aR,8aS)-6-(5-[4-(trifluoromethyl)phenyl]sulfonyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	929.2
5		(4aR,8aS)-6-(5-(2-chloro-4-fluorophenyl)sulfonyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	675.6
6		(4aR,8aS)-6-[(1R,5S,6r)-6-[1-(4-fluorophenyl)pyrazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	260.6

7		(4aR,8aS)-6-[(1R,5S,6r)-6-[1-[4-fluoro-3-(trifluoromethyl)phenyl]pyrazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	45.3
8		(4aR,8aS)-6-[(1R,5S,6r)-6-[1-(2-chloro-4-fluoro-phenyl)pyrazol-3-yl]-3-azabicyclo[3.1.0]hexane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	111.7
9		(4aR,8aS)-6-[rel-(1R,4R,5S)-5-(5,6,7,8-tetrahydroisoquinolin-3-ylmethoxy)-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	76.0
10		(4aR,8aS)-6-[rel-(1R,4R,5S)-5-(5-chloro-4-cyclopropyl-2-pyridyl)methoxy]-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	16.2

11		(4aR,8aS)-6-[rel-(1R,4R,5S)-5-[(5-chloro-4-cyclopropyl-2-pyridyl)methoxy]-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	82.5
12		(4aR,8aS)-6-[(1R,5S,6r)-6-[(2-chloro-4-fluoro-phenoxy)methyl]-3-azabicyclo[3.1.0]hexane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	6.3
13		(4aR,8aS)-6-[8-[(2-chloro-4-fluoro-phenoxy)methyl]-3-azabicyclo[3.2.1]octane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	5.1
14		(4aR,8aS)-6-[5-(2-chloro-4-fluoro-phenoxy)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	3.5
15		(4aR,8aS)-6-[5-[(2-chloro-4-fluoro-phenyl)methoxy]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	11.0
16		(4aR,8aS)-6-[5-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-carbonyl]-	85.9

		4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	
17		(4aR,8aS)-6-[5-[2-fluoro-4-(trifluoromethyl)phenoxy]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	4.7
18		(4aR,8aS)-6-[rel-(1R,4S,6S)-6-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	1049.4
19		(4aR,8aS)-6-[rel-(1R,4S,6R)-6-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	1142.2
20		(4aR,8aS)-6-[rel-(1R,4R,5S)-5-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	9.7
21		(4aR,8aS)-6-[rel-(1R,4R,5S)-5-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	18.6

22		(4aR,8aS)-6-[6-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-3-azabicyclo[3.1.1]heptane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	217.3
23		(4aR,8aS)-6-[(1S,5R)-7-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-3-oxa-9-azabicyclo[3.3.1]nonane-9-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	628.5
24		(4aR,8aS)-6-[(1S,5R)-3-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-8-azabicyclo[3.2.1]octane-8-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	1.4
25		(4aR,8aS)-6-[(1R,5S,6r)-6-[[2-fluoro-4-(trifluoromethyl)phenoxy]methyl]-3-azabicyclo[3.1.0]hexane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	32.0
26		(4aR,8aS)-6-[3-[(2-chloro-4-fluoro-phenoxy)methyl]-8-azabicyclo[3.2.1]octane-8-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	3694.0

27		(4aS,8aR)-6-[8-[(2-chloro-4-fluoro-phenoxy)methyl]-3-azabicyclo[3.2.1]octane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	669.7
28		(4aR,8aS)-6-[rel-(1R,4R,5S)-5-(5,6,7,8-tetrahydroisoquinolin-3-ylmethoxy)-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one	54.5

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 IC_{50} 's for MAGL inhibition below 25 μM , preferably below 10 μM , more preferably below 5 μM as measured in the MAGL assays described herein.

In one embodiment, compounds of formula (I) and their pharmaceutically acceptable salts or esters as described herein have IC_{50} (MAGL inhibition) values between 0.000001 μM and 25 μM , particular compounds have IC_{50} values between 0.000005 μM and 10 μM , further particular compounds have IC_{50} values between 0.00005 μM and 5 μM , as measured in the MAGL assays described herein.

Using the Compounds of the Invention

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

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

- 37 -

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

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

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

In one aspect, the present invention provides the use of compounds of formula (I) 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,
15 anxiety, migraine, 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 formula (I)
20 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) as described herein for the treatment or prophylaxis of multiple sclerosis in a mammal.

25 In one aspect, the present invention provides compounds of formula (I) 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.

- 38 -

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

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

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

In one aspect, the present invention provides compounds of formula (I) 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,
15 anxiety, migraine, 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 compounds of formula (I) as
20 described herein for use in 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 compounds of formula (I) as described herein for use in the treatment or prophylaxis of multiple sclerosis in a mammal.

In one aspect, the present invention provides the use of compounds of formula (I) as described
25 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.

- 39 -

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

In one embodiment, the present invention provides the use of compounds of formula (I) 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) as described herein for the preparation of a 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) 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, stroke, epilepsy, anxiety, migraine, 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 formula (I) 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) as described 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

- 40 -

inflammatory bowel disease in a mammal, which method comprises administering an effective amount of a compound of formula (I) 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
5 administering an effective amount of a compound of formula (I) 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) as described herein to the mammal.

10 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) as described herein to the mammal.

In one embodiment, the present invention provides a method for the treatment or prophylaxis of inflammatory bowel disease in a mammal, which method comprises administering an effective
15 amount of a compound of formula (I) 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 amount of a compound of formula (I) as described herein to the mammal.

In a further aspect, the present invention provides a method for the treatment or prophylaxis of
20 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 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,
25 which method comprises administering an effective amount of a compound of formula (I) as 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) as
30 described herein to the mammal.

- 41 -

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) as described herein to the mammal.

5 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.

Exemplary, yet non-limiting examples of possible pharmaceutical compositions comprising compounds of formula (I) are described in Examples 29 and 30.

- 10 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
15 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
20 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,
25 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.

- 42 -

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.

- 5 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
10 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
15 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.

General Methods:

- 20 **A1 (illustrated for example 3)**

- To an ice-cold solution of bis(trichloromethyl) carbonate (28.8 mg, 97.1 μ mol) in DCM (1.83 ml) were added sodium bicarbonate (46.6 mg, 555 μ mol) and (4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one acetate (**BB1**, 30 mg, 139 μ mol) and the mixture was stirred overnight at room temperature. To the suspension was added (3aR,6aS)-2-
25 (phenylsulfonyl)octahydropyrrolo[3,4-c]pyrrole hydrochloride (**BB5**, 40.1 mg, 139 μ mol) and DIPEA (71.7 mg, 96.9 μ l, 555 μ mol). The suspension was stirred at RT for 1.5 hours. The reaction mixture was poured on water and DCM and the layers were separated. The aqueous layer was extracted three times with DCM. The organic layers were washed twice with water, dried over MgSO_4 , filtered, treated with silica gel and evaporated. The compound was purified

- 43 -

by prep HPLC (Method B3) to get the desired compound as a white solid (44 mg; 73%). LC-MS (ESI): $[M+H]^+ = 435.2$ m/z

A2 (illustrated for example 1)

5 5-(2-chlorophenoxy)octahydrocyclopenta[c]pyrrole HCl (CAS 1889054-91-4, 45 mg, 164 μ mol) was dissolved in acetonitrile (0.5 ml). 4-nitrophenyl (4aR,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (**BB2**, 52.7 mg, 164 μ mol) and DIPEA (63.6 mg, 86 μ l, 492 μ mol) were added at room temperature, followed by stirring at 80°C for 20h. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC (method B1). The
10 purified product was concentrated *in vacuo* to afford (4aR,8aS)-6-(5-(2-chlorophenoxy)octahydrocyclopenta[c]pyrrole-2-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (5 mg, 7.26 % yield) as a colorless solid. LC-MS (ESI): $[M+H]^+ = 420.2$ m/z

A3 (illustrated for example 12)

A microwave vial was heat gun-dried and charged with bis(trichloromethyl) carbonate (26.6 mg, 89.6 μ mol) and sodium bicarbonate (32.3 mg, 384 μ mol). The flask was placed under argon and DCM (1 ml) was added to give a suspension. The suspension was cooled by an ice-bath and (1R,5S,6r)-6-((2-chloro-4-fluorophenoxy)methyl)-3-azabicyclo[3.1.0]hexane hydrochloride
20 (**BB13**, 35.6 mg, 128 μ mol) was added to the reaction. The mixture was stirred at 0 °C for 15 min and at room temperature overnight. The suspension turned into a clear solution overnight. The reaction mixture was then cooled down in an-ice bath and DCM (500 μ l) and DIPEA (49.7 mg, 67.1 μ l, 384 μ mol) followed by (4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (**BB1**, 20 mg, 128 μ mol) were added. The resulting off-white suspension was stirred at room
25 temperature for 6 hours.

The reaction mixture was poured on water and DCM and the layers were separated. The aqueous layer was extracted twice with DCM. The organic layers were dried over MgSO₄, filtered and evaporated to afford an orange oil (60 mg). The crude was purified by reverse-phase HPLC (method B7) to afford 24 mg (44.2%) of (4aR,8aS)-6-[(1R,5S,6r)-6-[(2-chloro-4-fluorophenoxy)methyl]-3-azabicyclo[3.1.0]hexane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one as a white solid after lyophilisation. LC-MS (ESI): $[M+H]^+ = 424.2$ m/z
30

HPLC Method B1

- 44 -

YMC-Triart C18, 12 nm, 5 μ m, 100 x 30 mm, 15 min run time, gradient 15-35-50-100% ACN in Water + 0.1% HCOOH

HPLC Method B2

- 5 YMC-Triart C18, 12 nm, 5 μ m, 100 x 30 mm, 15 min run time, gradient 30-50-65-100% ACN in Water + 0.1% HCOOH

HPLC Method B3

Gemini NX, 12 nm, 5 μ m, 100 x 30 mm, 15 min gradient, ACN / Water + 0.1% TEA

10

HPLC Method B4

YMC-Triart C18, 12 nm, 5 μ m, 100 x 30 mm, 11 min run time, gradient 15-35-50-100% ACN in Water + 0.1% TEA

- 15 **HPLC Method B5**

YMC-Triart C18, 12 nm, 5 μ m, 100 x 30 mm, 9 min run time, gradient 40-60-80-100% ACN in Water + 0.1% HCOOH

HPLC Method B6

- 20 YMC-Triart C18, 12 nm, 5 μ m, 100 x 30 mm, 11 min run time, gradient 20-40-55-100% ACN in Water + 0.1% HCOOH

HPLC Method B7

Gemini NX, 12 nm, 5 μ m, 100 x 30 mm, 15 min gradient, ACN / Water + 0.1% HCOOH

25

HPLC Method B8 (chiral)

Chiralpak AD, Normal Phase (isocratic): 65% Heptane; 35% Ethanol + NH₄Oac

HPLC Method B9

- 30 Gemini NX, 12 nm, 5 μ m, 100 x 30 mm, 15 min run time, gradient 30-50-65-100% ACN in Water + 0.1% HCOOH

Chiral SFC Method C1

- 45 -

OD-H, 12 nm, 5 μ m, 250 x 4.6 mm, 30% iPrOH**Chiral SFC Method C2**AD-H, 12 nm, 5 μ m, 250 x 4.6 mm, 40% MeOH

5

Chiral SFC Method C3OZ-H, 12 nm, 5 μ m, 250 x 4.6 mm, 35% iPrOH + 0.2% DEA**Chiral SFC Method C4**10 IB, 12 nm, 5 μ m, 250 x 4.6 mm, 9% MeOH, 100 ml/min**Chiral SFC Method C5**IC, 12 nm, 5 μ m, 250 x 4.6 mm, 30% MeOH

Ex.	Building Blocks	Synthesis and Purification Method	ESI(MS)
1	BB2a	A2	m/z = 420.2[M+H ⁺] ⁺
	CAS: 1889054-91-4	B1	
2	BB2a	A2	m/z = 400.3 [M+H ⁺] ⁺
	CAS: 1893326-25-4	B2	
3	BB1a	A1	m/z = 435.2 [M+H ⁺] ⁺
	CAS: 1422449-96-4	B3	
4	BB1a	A1	m/z = 503.3 [M+H ⁺] ⁺
	CAS: 1825117-24-5	B4	
5	BB1a	A1	m/z = 487.1 [M+H ⁺] ⁺
	CAS: 1822096-52-5	B5	

- 46 -

6	BB1a CAS: 2075635-92-4	A1 B1	m/z = 426.3 [M+H ⁺] ⁺
7	BB1a BB9	A1 B2	m/z = 494.3 [M+H ⁺] ⁺
8	BB1a BB10	A1 B6	m/z = 460.2 [M+H ⁺] ⁺
9	BB2a BB11	A2 C1 Product is the first eluting of the two diastereomers.	m/z = 441.3 [M+H ⁺] ⁺
10	BB2a BB12	A2 C2 Product is the first eluting of the two diastereomers.	m/z = 461.3 [M+H ⁺] ⁺
11	BB2a BB12	A2 C2 Product is the second eluting of the two diastereomers.	m/z = 461.3 [M+H ⁺] ⁺
12	BB1a BB13	A3 B7	m/z = 424.2 [M+H ⁺] ⁺
13	BB2a BB14	A2 B7	m/z = 452.2 [M+H ⁺] ⁺

- 47 -

14	BB2a	A2	m/z = 438.3
	BB15	B3	[M+H ⁺] ⁺
15	BB1a	A1	m/z = 452.18
	BB16	flash chromatography (SiO ₂ , 0% to 10% MeOH in DCM)	[M+H ⁺] ⁺
16	BB1a	A1	m/z = 486.20
	BB17	flash chromatography (SiO ₂ , 0% to 10% MeOH in DCM)	[M+H ⁺] ⁺
17	BB1a	A1	m/z = 472.19
	BB18	flash chromatography (SiO ₂ , 0% to 10% MeOH in DCM)	[M+H ⁺] ⁺
18	BB1a	A1	m/z = 472.3
	BB19	B8 Product is the second eluting of the two diastereomers.	[M+H ⁺] ⁺
19	BB1a	A1	m/z = 472.3
	BB20	B8 Product is the second eluting of the two diastereomers.	[M+H ⁺] ⁺
20	BB1a	A1	m/z = 472.4
	BB21	C3 Product is the first eluting of the two diastereomers.	[M+H ⁺] ⁺

- 48 -

21	BB1a	A1	m/z = 472.4 [M+H ⁺] ⁺
	BB21	C3 Product is the second eluting of the two diastereomers.	
22	BB1a	A1	m/z = 472.2 [M+H ⁺] ⁺
	BB22	flash chromatography (SiO ₂ , 0% to 10% MeOH in DCM)	
23	BB1a	A1	m/z = 502.20 [M+H ⁺] ⁺
	BB23	flash chromatography (SiO ₂ , 0% to 10% MeOH in DCM)	
24	BB1a	A1	m/z = 486.41 [M+H ⁺] ⁺
	BB24	flash chromatography (SiO ₂ , 0% to 10% MeOH in DCM)	
25	BB1a	A1	m/z = 458.17 [M+H ⁺] ⁺
	BB25	flash chromatography (SiO ₂ , 0% to 10% MeOH in DCM)	
26	BB2a	A2	m/z = 452.2 [M+H ⁺] ⁺
	BB26	B9	
27	BB2b	A2	m/z = 452.2 [M+H ⁺] ⁺
	BB14	B7	
28	BB2a	A2	m/z = 441.3 [M+H ⁺] ⁺
	BB11	C1 Product is the second eluting of the two diastereomers.	

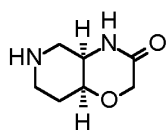
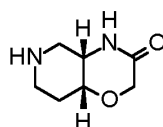
- 49 -

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 (-)**

The enantiomers of rac-(4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one dihydrochloride (BB1, CAS 1909295-00-6, 500 mg, 2.18 mmol) were separated by preparative chiral HPLC (ReprosilChiral NR column) using an isocratic mixture of EtOH (containing 0.05% of NH₄OAc) : n-heptane (30 : 70).

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]⁺.

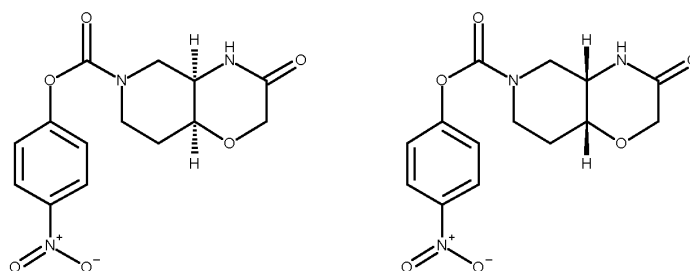
BB2a & BB2b

(4-nitrophenyl) (4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate

and

(4-nitrophenyl) (4aS,8aR)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate

- 50 -



A suspension of rac-(4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one dihydrochloride (**BB1**, 4.5 g, 19.6 mmol) in dry DCM (125 ml) was cooled down to 0°C and DIPEA (6.35 g, 8.58 ml, 49.1 mmol) was added, followed by 4-nitrophenyl carbonochloridate (4.35 g, 21.6 mmol). The reaction mixture was stirred at 0°C for 10 min and for 2 hours at room temperature. The crude reaction was diluted with dichloromethane, transferred into a separating funnel for extraction with sat. aq. Na₂CO₃. The organic phase was collected and the aqueous phase was back-extracted with dichloromethane. The combined organic phases were dried over sodium sulfate and evaporated down to dryness to yield 6.62 g of a crude racemic product as a yellow solid. The crude material was directly submitted for a chiral SFC separation (Method C4) to yield the two enantiomers:

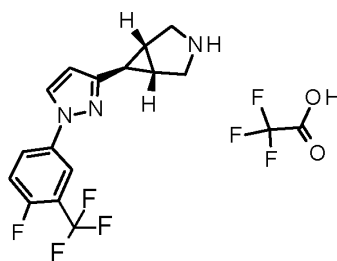
First eluting enantiomer, light beige solid (3.25g), contaminated with the second enantiomer.

The fraction was submitted for another SFC chiral separation (Method C5) to yield 2.71 g of the desired enantiomer (**BB2a**).

Second eluting enantiomer, yellow solid (**BB2b**, 2.72 g)

BB9

(1R,5S,6r)-6-[1-[4-fluoro-3-(trifluoromethyl)phenyl]pyrazol-3-yl]-3-azabicyclo[3.1.0]hexane 2,2,2-trifluoroacetate



- 51 -

In a 20 ml tube under argon, tert-butyl (1R,5S,6r)-6-(1-(4-fluorophenyl)-1H-pyrazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (120mg, 349 μ mol) was dissolved in DCM (2 ml), TFA (239 mg, 162 μ l, 2.1 mmol) was added and the reaction stirred at room temperature for 16hr, and then concentrated *in vacuo* (azeotrop with toluene) to yield the desired product (122 mg, 98%).

5 Used directly in next step. LC-MS (ESI): $m/z = 244.2 [M+H]^+$

a) tert-butyl (1R,5S,6r)-6-((E)-3-(dimethylamino)acryloyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

tert-butyl (1R,5S,6r)-6-acetyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (CAS 2075712-96-6, 990 mg, 4.39 mmol) was combined with N,N-dimethylformamide dimethyl acetal (3.24 g, 3.64 ml, 26.4 mmol) and heated at 100°C over night for 15 hrs. The mixture was cooled to room temperature and directly evaporated *in vacuo*. The residue was extracted with ethyl acetate / water, brine, organic fractions were combined and dried over MgSO₄, filtered and concentrated under reduced pressure to afford the desired product (1.21 g, 98%) as a yellow oil, LC-MS (ESI): $m/z = 281.3 [M+H]^+$

15 *b) tert-butyl (1R,5S,6r)-6-(1H-pyrazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate*

In a 20ml tube, tert-butyl (1R,5S,6r)-6-((E)-3-(dimethylamino)acryloyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (1.21 g, 4.32 mmol) was dissolved in ethanol (6 ml) and hydrazine hydrate (302 mg, 293 μ l, 6.04 mmol) was added. The reaction was stirred 1 hr at 80°C. Solvent was removed under reduced pressure, purification by preparative SFC (Princeton 20 2-Ethyl Pyridine column, 30x250 mm, 5% EtOH + 0.2% DEA) yielded the desired product as a yellow, viscous oil (890 mg, 83%). LC-MS (ESI): $m/z = 250.1 [M+H]^+$

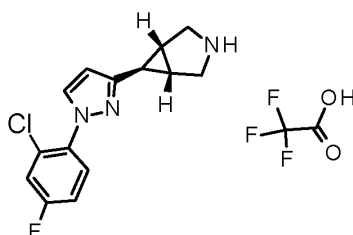
c) tert-butyl (1R,5S,6r)-6-(1-(4-fluorophenyl)-1H-pyrazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

In a 100 ml flask under argon, tert-butyl (1R,5S,6r)-6-(1H-pyrazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (300mg, 1.2 mmol) was suspended in DMF (8 ml), pyridine (381 mg, 389 μ l, 4.81 mmol), (4-fluorophenyl)boronic acid (219 mg, 1.56 mmol) and copper (II) acetate (328 mg, 1.8 mmol) were added. The green solution was stirred 60 hr at room temperature. Solvent was removed *in vacuo*, the crude was extracted with ethyl acetate / water / sat. NaCl, organic fractions were dried over MgSO₄, filtered and solvent was removed. 25 Purification by flash chromatography (SiO₂, Heptane / ethyl acetate 0 to 40% in 40min) led to the desired product as a colorless, solid (317 mg, 77%). LC-MS (ESI): $m/z = 288.1 [M-56+H]^+$

- 52 -

BB10

(1R,5S,6r)-6-[1-[2-chloro-4-fluoro-phenyl]pyrazol-3-yl]-3-azabicyclo[3.1.0]hexane 2,2,2-trifluoroacetate

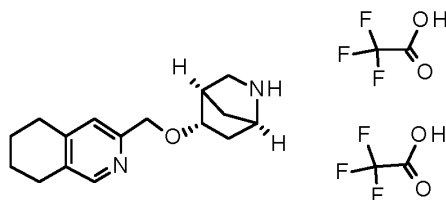


- 5 BB10 was prepared similarly as described for BB9, using tert-butyl (1R,5S,6r)-6-(1H-pyrazol-3-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate and (2-chloro-4-fluorophenyl)boronic acid in step c).

LC-MS (ESI) for BB10: $m/z = 278.2$ $[M+H]^+$

BB11

- 10 rac-3-((((1R,4R,5S)-2-azabicyclo[2.2.1]heptan-5-yl)oxy)methyl)-5,6,7,8-tetrahydroisoquinoline bis(2,2,2-trifluoroacetate)



- In a 20 ml tube under argon, rac-tert-butyl (1R,4R,5S)-5-((5,6,7,8-tetrahydroisoquinolin-3-yl)methoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate (40mg, 112 μ mol) was dissolved in
 15 DCM (1 ml), TFA (69 μ l, 0.89 mmol) was added and the reaction stirred at room temperature for 24 hr, and then concentrated *in vacuo* (azeotrop with toluene) to yield the desired product (60 mg, 90% pure, 99.5%) as a light yellow oil. Used directly in next step. LC-MS (ESI): $m/z = 259.3$ $[M+H]^+$

a) 3-(bromomethyl)-5,6,7,8-tetrahydroisoquinoline

- 53 -

Appel reaction: To a solution of (5,6,7,8-tetrahydroisoquinolin-3-yl)methanol (169 mg, 1.04 mmol) in dry DCM (2.91 ml) was added CBr₄ (412 mg, 1.24 mmol), the mixture was cooled to 0-3°C and within 10 min triphenylphosphine (353 mg, 1.35 mmol) in 1ml dry DCM was added. Stirring continued for 1 hr at 2-4°C, then 20ml DCM and silica gel were added, the solvent was removed *in vacuo* and the crude was purified by flash chromatography (SiO₂, heptane/ethylacetate 0 to 50% in 40min). The desired product was obtained as 190 mg (81%) of a light red solid. LC-MS (ESI): m/z = 226.1 [M+H]⁺

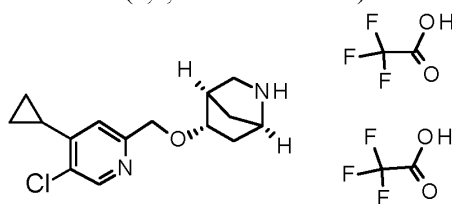
b) rac-tert-butyl (1R,4R,5S)-5-((5,6,7,8-tetrahydroisoquinolin-3-yl)methoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate

To a solution of rac-tert-butyl (1S,4S,5R)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (CAS 198835-03-9, 197 mg, 924 μmol) in dry THF (2.79 ml) was added potassium tert-butoxide 1M in THF (924 μl, 924 μmol) and the turbid reaction mixture was stirred at r.t. for 30 min followed by addition of 3-(bromomethyl)-5,6,7,8-tetrahydroisoquinoline (190 mg, 840 μmol) at 0-2°C. The reaction mixture was 3 hr stirred at 3-6°C, then diluted with ethyl acetate and extracted with water, the organic phase was collected and the aqueous phase was back-extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated down to dryness. The crude material was purified by prep. HPLC (Gemini NX, 12 nm, 5 μm, 100 x 30 mm, ACN / Water+0.1% TEA) to get the desired product (40 mg, 13.3%) as a light brown solid. LC-MS (ESI): m/z = 359.3 [M+H]⁺

20

BB12

rac-(1R,4R,5S)-5-[(5-chloro-4-cyclopropyl-2-pyridyl)methoxy]-2-azabicyclo[2.2.1]heptane bis(2,2,2-trifluoroacetate)



In a 20 ml tube under argon, rac-tert-butyl (1R,4R,5S)-5-((5-chloro-4-cyclopropylpyridin-2-yl)methoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate (272mg, 718 μmol) was dissolved in DCM (2 ml), TFA (332 μl, 0.4.3 mmol) was added and the reaction stirred at room temperature for 24 hr, and then concentrated *in vacuo* (azeotrop with toluene) to yield the desired product

25

- 54 -

(381 mg, 90% pure, 94%) as a light yellow oil. Used directly in next step. LC-MS (ESI): $m/z = 279.2 [M+H]^+$

a) 2-(bromomethyl)-5-chloro-4-cyclopropylpyridine

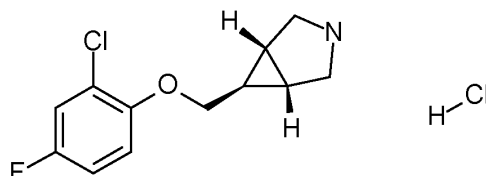
Appel reaction: To a solution of (5-chloro-4-cyclopropylpyridin-2-yl)methanol (290 mg, 1.58 mmol) in dry DCM (5 ml) was added $CBBr_4$ (628 mg, 1.9 mmol), the mixture was cooled to 0-3°C and within 10 min triphenylphosphine (538 mg, 2.05 mmol) in 1ml dry DCM was added. Stirring continued for 1 hr at 2-4°C, then 20ml DCM and silica gel were added, the solvent was removed *in vacuo* and the crude was purified by flash chromatography (SiO_2 , heptane/ethylacetate 0 to 40% in 40min). The desired product was obtained as 345 mg (90% pure, 80%) of a light red semisolid. LC-MS (ESI): $m/z = 248.0 [M+H]^+$

b) rac-tert-butyl (1R,4R,5S)-5-((5-chloro-4-cyclopropylpyridin-2-yl)methoxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate

To a solution of tert-butyl 5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (CAS 198835-03-9, 324 mg, 1.52 mmol) in dry THF (5 ml) was added potassium tert-butoxide 1M in THF (1.52 ml, 1.52 mmol) and the turbid reaction mixture was stirred at r.t. for 30 min followed by addition of 2-(bromomethyl)-5-chloro-4-cyclopropylpyridine (340 mg, 1.38 mmol) at 0-2°C. The reaction mixture was 3 hr stirred at 3-6°C, then diluted with ethyl acetate and extracted with water, the organic phase was collected and the aqueous phase was back-extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated down to dryness. The crude material was purified by flash chromatography (silica gel, 0% to 50% in 40min EtOAc in heptane) to get the desired product (272 mg, 95% pure, 49.4%) as a light brown oil. LC-MS (ESI): $m/z = 379.2 [M+H]^+$

BB13

(1R,5S,6r)-6-[(2-chloro-4-fluorophenoxy)methyl]-3-azabicyclo[3.1.0]hexane;hydrochloride



25

To a solution of tert-butyl (1R,5S,6r)-6-[(2-chloro-4-fluorophenoxy)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (150.0 mg, 0.440 mmol) in EtOAc (2 mL) was added 9M

- 55 -

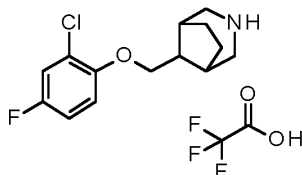
HCl in EtOAc (0.4 mL, 3.6 mmol) at 0 °C. The solution was stirred at 15 °C for 2.5 hrs. The solution was concentrated, then dried by lyophilization *in vacuo* to obtain desired product (1R,5S,6r)-6-[(2-chloro-4-fluorophenoxy)methyl]-3-azabicyclo[3.1.0]hexane hydrochloride (56.2 mg, 0.200 mmol, 44.94% yield as a white solid. LC-MS (ESI): $m/z = 242.0$ $[M+H]^+$

5 *a) tert-butyl (1R,5S,6r)-6-[(2-chloro-4-fluorophenoxy)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate*

To a solution of tert-butyl (1R,5S,6r)-6-(methylsulfonyloxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (CAS 958633-11-9, 294 mg, 1.01 mmol) in DMF (3 mL) was added cesium carbonate (493.16 mg, 1.51 mmol), 2-chloro-4-fluorophenol (0.11 mL, 1.11 mmol) at 15 °C. The mixture was heated to 85 °C and stirred for 16 hrs. The mixture was quenched with water (5 mL) at 0 °C, then extracted three times with EtOAc (5 mL) and dried over Na₂SO₄. The organic layers were combined and concentrated *in vacuo* to obtain crude product as a yellow oil. The crude product was purified by Prep-HPLC and dried by lyophilization to obtain the desired product tert-butyl (1R,5S,6r)-6-[(2-chloro-4-fluorophenoxy)methyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (150 mg, 0.440 mmol, 43.4% yield) as a light yellow oil. LC-MS (ESI): $m/z = 286.0$ $[M-56+H]^+$

BB14

8-[(2-chloro-4-fluorophenoxy)methyl]-3-azabicyclo[3.2.1]octane 2,2,2-trifluoroacetate



20 Boc-deprotection was performed as described e.g. for **BB12**. Crude product was obtained as a light yellow oil and was used directly for next step (Yield 99%, Purity 80%). LC-MS (ESI): $m/z = 270.2$ $[M+H]^+$

a) tert-butyl 8-((2-chloro-4-fluorophenoxy)methyl)-3-azabicyclo[3.2.1]octane-3-carboxylate

To a solution of 2-chloro-4-fluorophenol (65.6 mg, 48.8 μ l, 448 μ mol), tert-butyl 8-(hydroxymethyl)-3-azabicyclo[3.2.1]octane-3-carboxylate (108 mg, 448 μ mol) and triphenylphosphine (117 mg, 448 μ mol) in DCM (2.24 mL) was added DIAD (99.5 mg, 95.7 μ l, 492 μ mol) dropwise and the reaction was stirred for 19 h at rt. The reaction mixture was

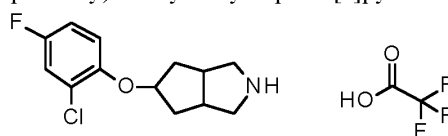
- 56 -

quenched by addition of sat. aq. NaHCO_3 solution. The phases were separated and the aq. phase was extracted with DCM three times. The combined organic layers were dried over sodium sulfate and concentrated to dryness to afford a brown oil. The crude was immobilized on Isolute and purified by column chromatography (SiO_2 , 0 - 30 % EtOAc in heptane) to afford tert-butyl 8-((2-chloro-4-fluorophenoxy)methyl)-3-azabicyclo[3.2.1]octane-3-carboxylate (45.9 mg, 26.3 %)

5 as a yellow oil. LC-MS (ESI): $m/z = 314.2$ $[\text{M}-56+\text{H}]^+$

BB15

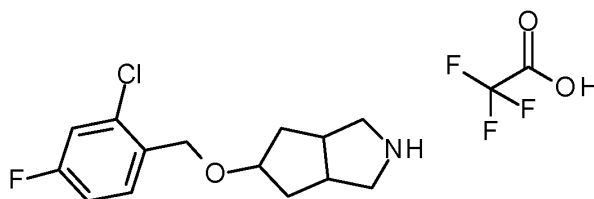
5-((2-chloro-4-fluorophenoxy)octahydrocyclopenta[c]pyrrole 2,2,2-trifluoroacetate



10 Synthesis was done as described for **BB14**, starting from 2-chloro-4-fluorophenol (64.5 mg, 440 μmol) and tert-butyl 5-hydroxyhexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (100 mg, 440 μmol). Product was obtained as a light-brown oil, yield after Boc-deprotection was 149.8 mg (purity 82%). LC-MS (ESI): $m/z = 256.2$ $[\text{M}+\text{H}]^+$

BB16

15 5-((2-chloro-4-fluorobenzyl)oxy)octahydrocyclopenta[c]pyrrole 2,2,2-trifluoroacetate



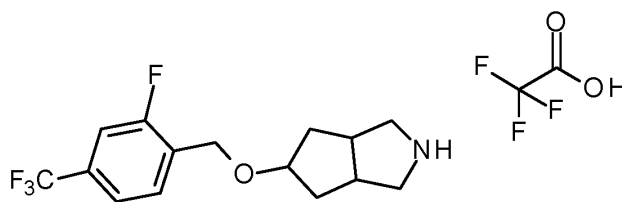
BB16 was prepared similarly as described for **BB11** (step b and Boc-deprotection), using tert-butyl 5-hydroxyhexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate and 1-(bromomethyl)-2-chloro-4-fluorobenzene.

20 LC-MS (ESI) for BB16: $m/z = 270.2$ $[\text{M}+\text{H}]^+$

BB17

5-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)octahydrocyclopenta[c]pyrrole 2,2,2-trifluoroacetate

- 57 -

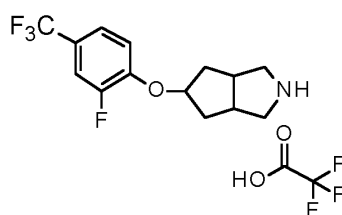


BB17 was prepared similarly as described for **BB11** (step b and Boc-deprotection), using tert-butyl 5-hydroxyhexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate and 1-(bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene.

5 LC-MS (ESI) for BB17: $m/z = 304.2 [M+H]^+$

BB18

5-(2-fluoro-4-(trifluoromethyl)phenoxy)octahydrocyclopenta[c]pyrrole 2,2,2-trifluoroacetate



In a 20 ml tube under argon, tert-butyl 5-(2-fluoro-4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (0.290 g, 745 μ mol) was dissolved in DCM (4 ml), TFA (574 μ l, 7.45 mmol) was added and the reaction stirred at room temperature for 1 hr, and then concentrated *in vacuo* (azeotrop with toluene) to yield the desired product (321 mg, 90% pure, 96%) as a colorless oil. Used directly in next step. LC-MS (ESI): $m/z = 290.2 [M+H]^+$

15 a) *tert-butyl 5-(2-fluoro-4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate*

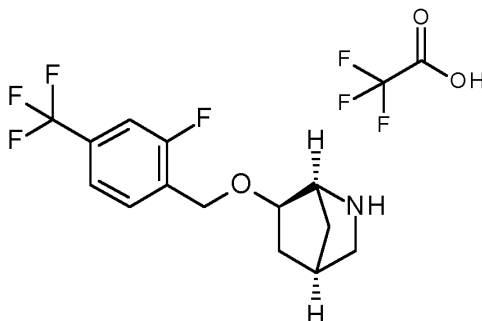
In a 25ml four-necked flask under argon, tert-butyl 5-hydroxyhexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (0.250 g, 1.1 mmol) was dissolved in THF (5 ml), and 2-fluoro-4-(trifluoromethyl)phenol (198 mg, 138 μ l, 1.1 mmol) and triphenylphosphine (317 mg, 1.21 mmol) were added. The clear solution was stirred 5 min at RT, then cooled to 0-2°C and slowly DEAD (211 mg, 192 μ l, 1.21 mmol) was added within 10min, stirring continued for 1 hr at 2-

- 58 -

4°C and overnight at RT. 50ml diethylether were added to the reaction mixture, which was extracted with 2x25ml water, 2x 20ml sat NaOH and 1x 20ml brine. The organic fraction was dried over Mg₂SO₄, solvent was removed *in vacuo*. The crude material was purified by flash chromatography (silica gel, 0% to 30% EtOAc in heptane), yielding the product as a colorless oil
 5 (290 mg, 67.7%). LC-MS (ESI): m/z = 334.2 [M-56+H⁺]⁺

BB19

Rac-(1S,4R,6R)-6-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)-2-azabicyclo[2.2.1]heptane 2,2,2-trifluoroacetate



10 Boc-deprotection was performed as described e.g. for **BB18**. Crude product was obtained as a light yellow oil and was used directly for next step (Yield 87%). LC-MS (ESI): m/z = 290.3 [M+H⁺]⁺

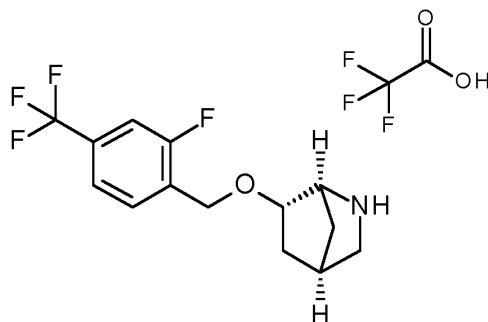
a) rac-tert-butyl (1R,4S,6S)-6-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate

15 To a solution of rac-tert-butyl (1R,4S,6S)-6-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (Synthonix, CAS 198835-05-1; 0.300 g, 1.41 mmol) in THF (5 ml) was added potassium tert-butoxide 1M solution in THF (1.48 ml, 1.48 mmol) and the turbid reaction mixture was stirred at r.t for 15min followed by addition of 1-(bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene (362 mg, 1.41 mmol). The reaction mixture was then stirred at r.t for 60 hr. The crude reaction was
 20 diluted with ethyl acetate and extracted with water, the organic phase was collected and the aqueous phase was back-extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated down to dryness. The crude material was purified by flash chromatography (silica gel, 0% to 80% EtOAc in heptane), yielding the desired product as a colorless oil (237 mg, 43%). LC-MS (ESI): m/z = 334.2 [M-56+H⁺]⁺

- 59 -

BB20

Rac-(1S,4R,6S)-6-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)-2-azabicyclo[2.2.1]heptane 2,2,2-trifluoroacetate

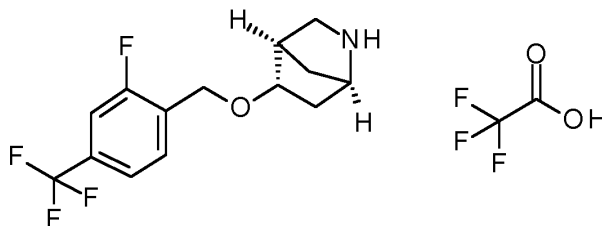


- 5 **BB20** was prepared similarly as described for **BB19**, using rac-tert-butyl (1R,4S,6R)-6-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (Combi-Blocks QE-8592, CAS : 207405-59-2) and 1-(bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene.

LC-MS (ESI) for BB20: $m/z = 290.3$ $[M+H]^+$

BB21

- 10 Rac-(1R,4R,5S)-5-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)-2-azabicyclo[2.2.1]heptane 2,2,2-trifluoroacetate



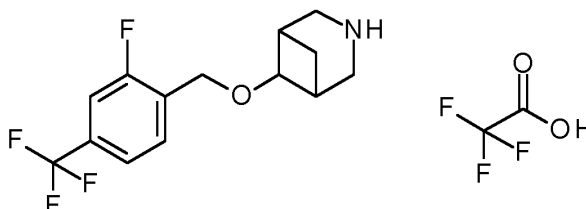
- BB21** was prepared similarly as described for **BB19**, using rac-tert-butyl (1R,4R,5S)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (AbovChem, CAS : 198835-03-9) and 1-(bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene.
- 15

LC-MS (ESI) for BB21: $m/z = 290.3$ $[M+H]^+$

BB22

- 60 -

6-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)-3-azabicyclo[3.1.1]heptane 2,2,2-trifluoroacetate

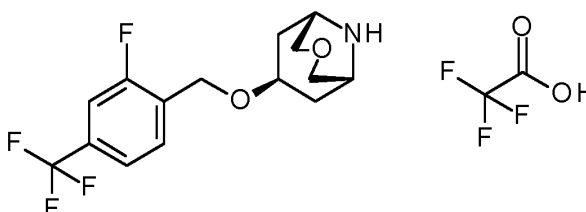


BB22 was prepared similarly as described for **BB19**, using tert-butyl 6-hydroxy-3-azabicyclo[3.1.1]heptane-3-carboxylate (Spirochem, CAS: 1357353-36-6) and 1-(bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene.

LC-MS (ESI) for BB21: $m/z = 290.2 [M+H]^+$

BB23

(1R,5S,7s)-7-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)-3-oxa-9-azabicyclo[3.3.1]nonane 2,2,2-trifluoroacetate



10

BB23 was prepared similarly as described for **BB19**, using tert-butyl (1R,5S,7s)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (endo, Spirochem, CAS: 1148006-31-8) and 1-(bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene.

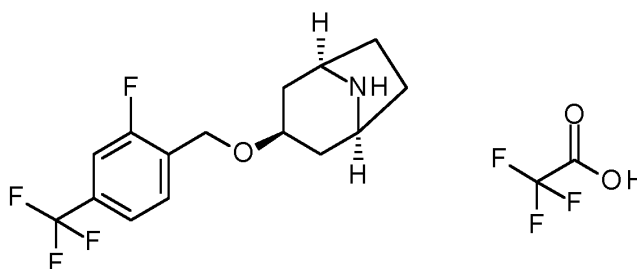
LC-MS (ESI) for BB21: $m/z = 320.2 [M+H]^+$

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BB24

(1R,3R,5S)-3-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)-8-azabicyclo[3.2.1]octane 2,2,2-trifluoroacetate

- 61 -

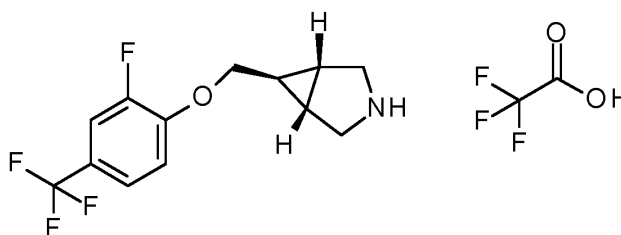


BB24 was prepared similarly as described for **BB19**, using tert-butyl (1R,3r,5S)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (endo, Spirochem, CAS: 143557-91-9) and 1-(bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene.

- 5 LC-MS (ESI) for BB21: $m/z = 304.2$ $[M+H]^+$

BB25

(1R,5S,6r)-6-((2-fluoro-4-(trifluoromethyl)phenoxy)methyl)-3-azabicyclo[3.1.0]hexane 2,2,2-trifluoroacetate



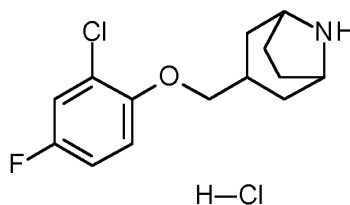
- 10 **BB25** was prepared similarly as described for **BB18**, using tert-butyl (1R,5S,6r)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate and 2-chloro-4-fluorophenol

LC-MS (ESI) for BB25: $m/z = 276.2$ $[M+H]^+$

BB26

3-((2-chloro-4-fluorophenoxy)methyl)-8-azabicyclo[3.2.1]octane hydrochloride

- 62 -



BB26 was prepared similarly as described for **BB13**, using tert-butyl 8-(methanesulfonyloxymethyl)-3-azabicyclo[3.2.1]octane-3-carboxylate and 2-chloro-4-fluorophenol

5 LC-MS (ESI) for BB26: $m/z = 270.0 [M+H]^+$

Example 29

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>
10 Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	<u>20 mg</u>
15	425 mg

Example 30

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

	<u>Per capsule</u>
20 Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	<u>0.5 mg</u>
25	220.0 mg