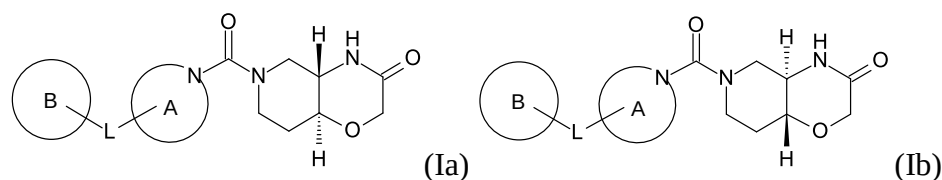


are driven mainly via cannabinoid receptors (CBRs), CB1 and CB2. CB1 receptors are present throughout the GI tract of animals and healthy humans, especially in the enteric nervous system (ENS) and the epithelial lining, as well as smooth muscle cells of blood vessels in the colonic wall (Wright K. *et 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.

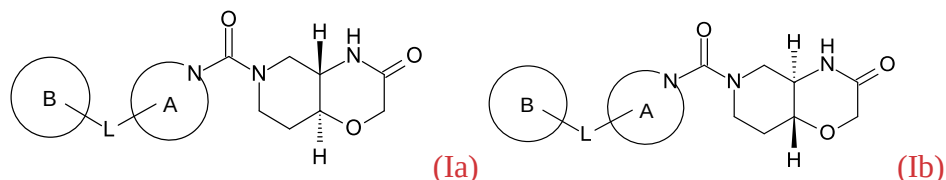
Summary of the Invention

In a first aspect, the present invention provides new heterocyclic compounds having the general formulae (Ia) and (Ib)



or pharmaceutically acceptable salts thereof, wherein A, B, and L are as described herein.

In one aspect, the present disclosure provides a compound of formula (Ia) or (Ib)



or a pharmaceutically acceptable salt thereof,

wherein:

A is a 3-14 membered heterocycle substituted with R^A;

B is C₆-C₁₄-aryl or 5-14 membered heteroaryl substituted with R¹, R² and R³;

L is selected from a covalent bond, -C≡C-, -CHR^L-, -CH₂CHR^L-, -O-, -OCH₂-, and -CH₂O-; and

R¹, R², and R³ are independently selected from hydrogen, halogen, cyano, C₁-C₆-alkylsulfonyl, R^bR^cN, C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkyl, halo-C₁-C₆-alkoxy, hydroxy-C₁-C₆-alkyl, C₆-C₁₄-aryl, C₃-C₁₀-cycloalkyl, 3-14 membered heterocyclyl, 5-14 membered heteroaryl, C₆-C₁₄-aryloxy, C₃-C₁₀-cycloalkyloxy, 3-14 membered heterocyclyloxy, and 5-14 membered heteroaryloxy, wherein said C₃-C₁₀-cycloalkyl, C₆-C₁₄-aryl, 3-14 membered heterocyclyl, 5-14 membered heteroaryl, C₆-C₁₄-aryloxy, C₃-C₁₀-cycloalkyloxy, 3-14 membered heterocyclyloxy, and 5-14 membered heteroaryloxy are optionally substituted with one or more substituents that are independently selected from halogen, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, and carbamoyl;

R^A is selected from hydrogen and C₁-C₆-alkyl;

R^b and R^c are independently selected from hydrogen, C₁-C₆-alkyl and C₆-C₁₄-aryl; and

R^L is selected from hydrogen, C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, alkoxy-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₆-C₁₄-aryl, and halo-C₆-C₁₄-aryl;

wherein the compound of formula (Ia) or (Ib) is not selected from:

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

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

rac-(4aS,8aS)-6-[4-(2-methylallyl)piperidine-1-carbonyl]-4,4a,5,7,8,8a-

hexahydropyrido[4,3-b][1,4]oxazin-3-one (CAS 1941372-36-6);

(+)-trans-6-[4-[[4-(Trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-

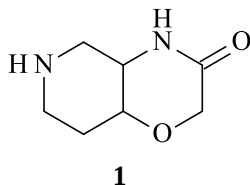
hexahydropyrido[4,3-b][1,4]oxazin-3-one; and

(-)-trans-6-[4-[[4-(Trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-

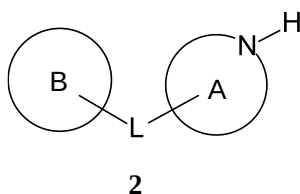
hexahydropyrido[4,3-b][1,4]oxazin-3-one.

In a further aspect, the~~The~~ present ~~invention~~disclosure provides a process of manufacturing the urea compounds of formula (Ia) or (Ib) described herein, comprising:

reacting a first amine 4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one (**1**)



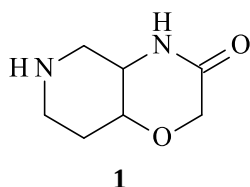
5 with a second amine of formula **2**, wherein A, L, and B are as described herein



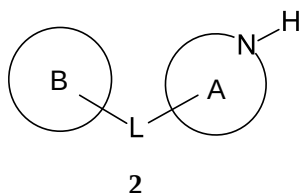
in the presence of a base and a urea forming reagent,
to form said compound of formula (Ia) or (Ib).

10 In a further aspect, the present disclosure provides a process of manufacturing the compounds of formula (Ia) or (Ib) as described herein, or pharmaceutically acceptable salts thereof, comprising:

reacting a first amine 4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one (**1**)



with a second amine of formula **2**, wherein A, L, and B are as described herein



15

in the presence of a base and a urea forming reagent,
to form said compound of formula (Ia) or (Ib).

~~In a further aspect, the~~The present ~~invention~~disclosure provides a compound of formula (Ia) or (Ib) as described herein, when manufactured according to the processes described herein.

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

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

~~In a further aspect, the~~The present ~~invention~~disclosure provides the use of a compound of formula (Ia) or (Ib) as described herein or of a pharmaceutical composition described herein for inhibiting monoacylglycerol lipase (MAGL) in a mammal.

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

In a further aspect, the present disclosure provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition 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.

In a further aspect, the present disclosure provides use of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, in 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.

~~In a further aspect, the~~The present ~~invention~~disclosure provides the use of a compound of formula (I) as described herein or of a pharmaceutical composition described herein for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral

sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, 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.

5 In a further aspect, the present disclosure provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein for use in the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis,
10 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 further aspect, the present disclosure provides use of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the
15 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
20 and/or visceral pain in a mammal.

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
25 understood to be applicable to any other aspect, embodiment or example described herein, unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of

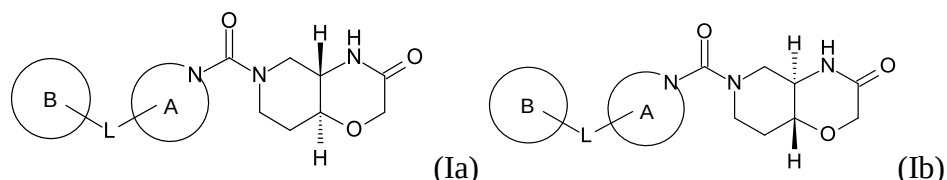
such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel 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 12 carbon atoms. In some preferred embodiments, the alkyl group contains 1 to 6 carbon atoms (“C₁₋₆-alkyl”), e.g., 1, 2, 3, 4, 5, or 6 carbon atoms. In other embodiments, the alkyl group contains 1 to 3 carbon atoms, e.g., 1, 2 or 3 carbon atoms. Some non-limiting examples of alkyl include methyl, ethyl, propyl, 2-propyl (isopropyl), n-butyl, isobutyl, sec-butyl, tert-butyl, and 2,2-dimethylpropyl. Particularly preferred, yet non-limiting examples of alkyl are methyl and tert-butyl.

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

CLAIMS

1. A compound of formula (Ia) or (Ib)



or a pharmaceutically acceptable salt thereof,

wherein:

A is a 3-14 membered heterocycle substituted with R^A ;

B is C_6 - C_{14} -aryl or 5-14 membered heteroaryl substituted with R^1 , R^2 and R^3 ;

L is selected from a covalent bond, $-C\equiv C-$, $-CHR^L-$, $-CH_2CHR^L-$, $-O-$, $-OCH_2-$, and $-CH_2O-$; and

R^1 , R^2 , and R^3 are independently selected from hydrogen, halogen, cyano, C_1 - C_6 -alkylsulfonyl, R^bR^cN , C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, halo- C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkoxy, hydroxy- C_1 - C_6 -alkyl, C_6 - C_{14} -aryl, C_3 - C_{10} -cycloalkyl, 3-14 membered heterocyclyl, 5-14 membered heteroaryl, C_6 - C_{14} -aryloxy, C_3 - C_{10} -cycloalkyloxy, 3-14 membered heterocyclyloxy, and 5-14 membered heteroaryloxy, wherein said C_3 - C_{10} -cycloalkyl, C_6 - C_{14} -aryl, 3-14 membered heterocyclyl, 5-14 membered heteroaryl, C_6 - C_{14} -aryloxy, C_3 - C_{10} -cycloalkyloxy, 3-14 membered heterocyclyloxy, and 5-14 membered heteroaryloxy are optionally substituted with one or more substituents that are independently selected from halogen, C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, halo- C_1 - C_6 -alkoxy, and carbamoyl;

R^A is selected from hydrogen and C_1 - C_6 -alkyl;

R^b and R^c are independently selected from hydrogen, C_1 - C_6 -alkyl and C_6 - C_{14} -aryl; and

R^L is selected from hydrogen, C_1 - C_6 -alkyl, hydroxy- C_1 - C_6 -alkyl, alkoxy- C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_6 - C_{14} -aryl, and halo- C_6 - C_{14} -aryl;

wherein the compound of formula (Ia) or (Ib) is not selected from:

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

(4aR,8aR)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
rac-(4aS,8aS)-6-[4-(2-methylallyl)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (CAS 1941372-36-6);
5 (+)-trans-6-[4-[[4-(Trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and
(-)-trans-6-[4-[[4-(Trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one.

2. ~~The compound of formula (Ia) or (Ib) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (Ia) or (Ib) is not selected from:~~

~~(4aS,8aS)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;~~
~~(4aR,8aR)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and~~
15 ~~rac-(4aS,8aS)-6-[4-(2-methylallyl)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (CAS 1941372-36-6).~~

3.2. The compound of formula (Ia) or (Ib) according to claim 1 ~~or 2~~, or a pharmaceutically acceptable salt thereof, wherein A is azetidine or 7-azaspiro[3.5]nonan-7-yl and R^A is hydrogen.

4.3. The compound of formula (Ia) or (Ib) according to ~~any one of claims 1 to 3~~claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein B is phenyl substituted with R¹, R² and R³.

5.4. The compound of formula (Ia) or (Ib) according to any one of claims 1 to ~~4~~3, or a pharmaceutically acceptable salt thereof, wherein:
L is selected from a covalent bond, -CHR^L-, -CH₂CH₂-, -O-, -OCH₂-, and -CH₂O-; and
R^L is hydrogen or halo-C₆-C₁₄-aryl.

6.5. The compound of formula (Ia) or (Ib) according to any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof, wherein L is selected from a covalent bond, -O-, -CH₂-, -CH₂CH₂-, and -CH₂O-.

7.6. The compound of formula (Ia) or (Ib) according to any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof, wherein L is a covalent bond or -O-.

8.7. The compound of formula (Ia) or (Ib) according to any one of claims 1 to 76, or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from halogen, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, halo-C₁-C₆-alkoxy, hydroxy-C₁-C₆-alkyl, C₆-C₁₄-aryloxy, C₆-C₁₄-aryl, and C₃-C₁₀-cycloalkyl, wherein said C₃-C₁₀-cycloalkyl, C₆-C₁₄-aryloxy and C₆-C₁₄-aryl are substituted with 1-2 substituents that are independently selected from halogen and halo-C₁-C₆-alkyl;

R² is selected from hydrogen and halogen; and

R³ is hydrogen.

9.8. The compound of formula (Ia) or (Ib) according to any one of claims 1 to 76, or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from C₆-C₁₄-aryloxy, halo-C₁-C₆-alkyl and C₃-C₁₀-cycloalkyl substituted with halo-C₁-C₆-alkyl;

R² is selected from hydrogen and halogen; and

R³ is hydrogen.

10.9. The compound of formula (Ia) or (Ib) according to any one of claims 1 to 76, or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from phenoxy, CF₃ and (trifluoromethyl)cyclopropyl;

R² is hydrogen or fluoro; and

R³ is hydrogen.

~~11. The compound of formula (Ia) or (Ib) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R² is selected from hydrogen and halogen.~~

~~12. The compound of formula (Ia) or (Ib) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R² is hydrogen or fluoro.~~

- ~~13. The compound of formula (Ia) or (Ib) according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.~~
- ~~14. The compound of formula (Ia) or (Ib) according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein:~~
- 5 ~~A is a 3-14 membered heterocycle;~~
- ~~B is C_6 - C_{14} -aryl substituted with R^1 and R^2 ;~~
- ~~L is selected from a covalent bond, $-CH_2CH_2-$, $-CHR^L-$, $-O-$ and $-CH_2O-$;~~
- ~~R^L is hydrogen or halo- C_6 - C_{14} -aryl;~~
- 10 ~~R^1 is selected from halogen, C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkoxy, hydroxy- C_1 - C_6 -alkyl, C_6 - C_{14} -aryloxy, C_6 - C_{14} -aryl, and C_3 - C_{10} -cycloalkyl, wherein said C_3 - C_{10} -cycloalkyl, C_6 - C_{14} -aryloxy and C_6 - C_{14} -aryl are substituted with 1-2 substituents that are independently selected from halogen and halo- C_1 - C_6 -alkyl; and~~
- ~~R^2 is selected from hydrogen and halogen.~~
- 15 ~~15. The compound of formula (Ia) or (Ib) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:~~
- ~~A is a 3-14 membered heterocycle;~~
- ~~B is C_6 - C_{14} -aryl substituted with R^1 and R^2 ;~~
- ~~L is a covalent bond or $-O-$;~~
- 20 ~~R^1 is selected from C_6 - C_{14} -aryloxy, halo- C_1 - C_6 -alkyl and C_3 - C_{10} -cycloalkyl substituted with halo- C_1 - C_6 -alkyl; and~~
- ~~R^2 is hydrogen or halogen.~~
- ~~16. The compound of formula (Ia) or (Ib) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:~~
- 25 ~~A is azetidine or 7-azaspiro[3.5]nonan-7-yl;~~
- ~~B is phenyl substituted with R^1 and R^2 ;~~
- ~~L is selected from a covalent bond, $-CH_2-$ or $-O-$;~~
- ~~R^1 is selected from phenoxy, CF_3 - and (trifluoromethyl)cyclopropyl; and~~
- ~~R^2 is hydrogen or fluoro.~~

~~17.10.~~ The compound of formula (Ia) or (Ib) according to ~~any one of claims 1 to 16~~claim 1, or a pharmaceutically acceptable salt thereof, selected from:~~the compounds disclosed in Table 1~~

(+)-trans-6-[3-(4-tert-Butylphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(-)-trans-6-[3-(4-tert-Butylphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(+)-trans-6-[3-[4-[1-(Trifluoromethyl)cyclopropyl]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(-)-trans-6-[3-[4-[1-(Trifluoromethyl)cyclopropyl]phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(+)-trans-6-[3-[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(-)-trans-6-[3-[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(+)-trans-6-[3-[3-Chloro-4-(trifluoromethoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(-)-trans-6-[3-[3-Chloro-4-(trifluoromethoxy)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(+)-trans-6-[3-[2-[2-Fluoro-4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(-)-trans-6-[3-[2-[2-Fluoro-4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(+)-trans-6-[3-(4-Phenoxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(-)-trans-6-[3-(4-Phenoxyphenyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(+)-trans-6-[3-[4-(2,4-Difluorophenyl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

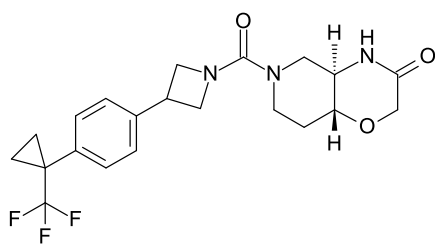
(-)-trans-6-[3-[4-(2,4-Difluorophenyl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

- (+)-trans-6-[3-[4-(2,2,2-Trifluoroethyl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (-)-trans-6-[3-[4-(2,2,2-Trifluoroethyl)phenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 5 (+)-trans-6-[6-[(2,4-Difluorophenyl)methyl]-2-azaspiro[3.3]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (-)-trans-6-[6-[(2,4-Difluorophenyl)methyl]-2-azaspiro[3.3]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (+)-trans-6-[3-[6-(2-Chlorophenoxy)-3-pyridyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 10 (-)-trans-6-[3-[6-(2-Chlorophenoxy)-3-pyridyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (+)-trans-6-[3-[[2-Chloro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (-)-trans-6-[3-[[2-Chloro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 15 (+)-trans-6-[3-[[4-(Trifluoromethoxy)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (-)-trans-6-[3-[[4-(Trifluoromethoxy)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 20 (+)-trans-6-[4-[Bis(4-fluorophenyl)methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (-)-trans-6-[4-[Bis(4-fluorophenyl)methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (+)-trans-6-[2-[2-Fluoro-4-(trifluoromethyl)phenoxy]-7-azaspiro[3.5]nonane-7-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 25 (-)-trans-6-[2-[2-Fluoro-4-(trifluoromethyl)phenoxy]-7-azaspiro[3.5]nonane-7-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (+)-trans-6-[4-[5-Chloro-1-(2-hydroxyethyl)indol-3-yl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 30 (-)-trans-6-[4-[5-Chloro-1-(2-hydroxyethyl)indol-3-yl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and

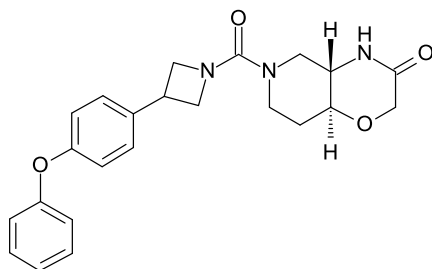
[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidin-1-yl]-[rac-(4aR,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-6-yl]methanone.

18.11. The compound of formula (Ia) or (Ib) according to ~~any one of claims 1 to 16~~claim 1, or a pharmaceutically acceptable salt thereof, selected from:

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

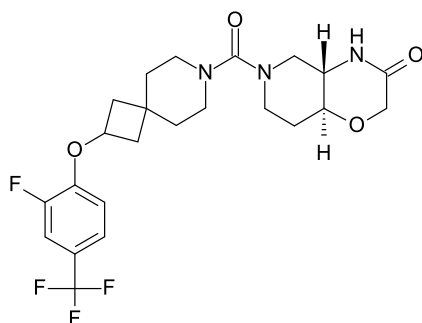


(4aS,8aS)-6-(3-(4-phenoxyphenyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one



10 ; and

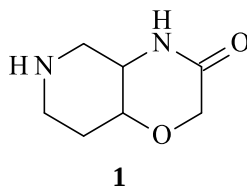
(-)- or (+)-trans-6-[2-[2-Fluoro-4-(trifluoromethyl)phenoxy]-7-azaspiro[3.5]nonane-7-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



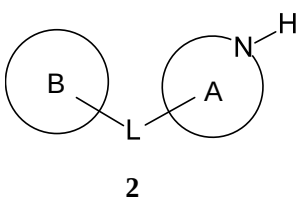
19.12. A process of manufacturing the compounds of formula (Ia) or (Ib) according to any one of claims 1 to ~~18~~11, or pharmaceutically acceptable salts thereof, comprising:

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reacting a first amine 4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one (1)



with a second amine of formula 2, wherein A, L, and B are as defined in any one of claims 1 to ~~18~~11



in the presence of a base and a urea forming reagent,
to form said compound of formula (Ia) or (Ib).

10 ~~20. — A compound of formula (Ia) or (Ib) according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, when manufactured according to the process of claim 19.~~

21,13. A compound of formula (Ia) or (Ib) according to any one of claims 1 to ~~18~~and 2011, or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance.

15 22,14. A pharmaceutical composition comprising a compound of formula (Ia) or (Ib) according to any one of claims 1 to ~~18 and 2011~~, or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier.

20 ~~23. — The use of a compound of formula (I) according to any one of claims 1 to 18 and 20, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 22 for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.~~

~~24. — The use of a compound of formula (I) according to any one of claims 1 to 18 and 20, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition~~

according to claim 22 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.

25.15. A compound of formula (I) according to any one of claims 1 to ~~18 and 2011~~, or a pharmaceutically acceptable salt thereof, or ~~of~~ a pharmaceutical composition according to claim ~~22-14~~ for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.

26.16. A compound of formula (I) according to any one of claims 1 to ~~18 and 2011~~, or a pharmaceutically acceptable salt thereof, or ~~of~~ a pharmaceutical composition according to claim ~~22-14~~ for use in the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic 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.

27.17. ~~The use~~Use of a compound of formula (I) according to any one of claims 1 to ~~18 and 2011~~, or a pharmaceutically acceptable salt thereof, ~~for in~~ 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.

28.18. ~~The use~~Use of a compound of formula (I) according to any one of claims 1 to ~~18 and 2011~~, or a pharmaceutically acceptable salt thereof, ~~for in~~ 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.

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~~29.—A method for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders, and/or inflammatory bowel disease in a mammal, which method comprises administering an effective amount of a compound of formula (I) according to any one of claims 1 to 18 and 20, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 22 to the mammal.~~

~~30.—A method for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain, spasticity associated with pain in a mammal, abdominal pain, abdominal pain associated with irritable bowel syndrome and/or visceral pain which method comprises administering an effective amount of a compound of formula (I) according to any one of claims 1 to 18 and 20, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 22 to the mammal.~~