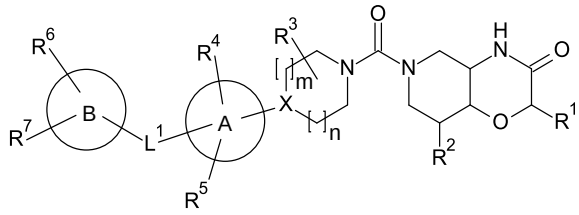
2009, *140*(1), 49-61; Nomura DK *et al.*, *Chem. Biol.* **2011**, *18*(7), 846-856, Jinlong Yin *et al*, *Nature Communications* **2020**, *11*, 2978).

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

In conclusion, suppressing the action and/or the activation of MAGL is a promising new therapeutic strategy for the treatment or prevention of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders, inflammatory bowel disease, 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~~

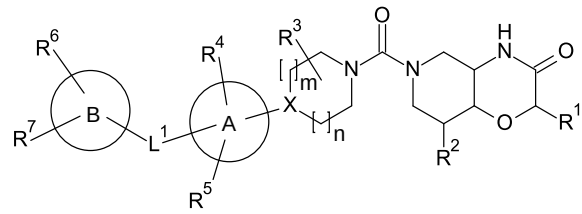
~~In a first aspect, the~~The present ~~invention~~disclosure provides compounds of formula (I)



(I)

wherein A, B, L^1, X, m, n, and R^1 to R^7 are as defined herein.

In one aspect, the present disclosure provides a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A is selected from C_6-C_{14}-aryl, 5- to 14-membered heteroaryl and 3- to 14-membered heterocyclyl;

B is

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

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

m is 0, n is 0 or 1 and X is CR^8; or

m is 1, n is 1 or 2 and X is CR^8 or N;

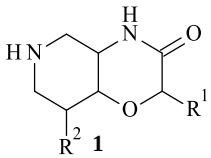
R^1, R^2, and R^3 are independently selected from hydrogen and C_{1-6}-alkyl;

R^4, R^5, R^6 and R^7 are independently selected from hydrogen, halogen, cyano, hydroxy, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, amino-C_{1-6}-alkoxy, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl, C_{1-6}-alkylsulfonyl, SF_5, carbamoyl, C_{3-10}-cycloalkyl-C_{1-6}-alkoxy–, C_{1-6}-alkyl-NH-C(O)–, C_{1-6}-alkyl-C(O)-NH–, and C_{3-10}-cycloalkyl, wherein each C_{3-10}-cycloalkyl is optionally substituted with 1-2 substituents selected from C_{1-6}-alkyl and halo-C_{1-6}-alkyl; and

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

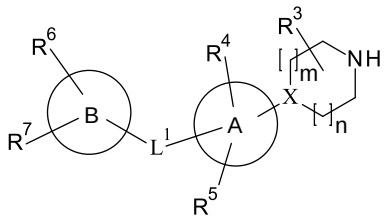
In a further aspect, the present ~~invention~~disclosure provides a process of manufacturing the compounds of formula (I) as described herein, or pharmaceutically acceptable salts thereof, comprising:

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



1

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



2

in the presence of a base and a urea forming reagent,

to form said compounds of formula (I) or pharmaceutically acceptable salts thereof,.

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

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

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

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

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

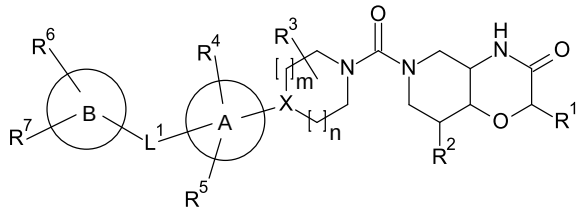
Detailed Description of the Invention

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 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.

CLAIMS

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A is selected from C_6-C_{14}-aryl, 5- to 14-membered heteroaryl and 3- to 14-membered heterocyclyl;

B is

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

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

m is 0, n is 0 or 1 and X is CR^8; or

m is 1, n is 1 or 2 and X is CR^8 or N;

R^1, R^2, and R^3 are independently selected from hydrogen and C_{1-6}-alkyl;

R^4, R^5, R^6 and R^7 are independently selected from hydrogen, halogen, cyano, hydroxy, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, amino-C_{1-6}-alkoxy, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl, C_{1-6}-alkylsulfonyl, SF_5, carbamoyl, C_{3-10}-cycloalkyl-C_{1-6}-alkoxy–, C_{1-6}-alkyl-NH-C(O)–, C_{1-6}-alkyl-C(O)-NH–, and C_{3-10}-cycloalkyl, wherein each C_{3-10}-cycloalkyl is optionally substituted with 1-2 substituents selected from C_{1-6}-alkyl and halo-C_{1-6}-alkyl; and

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

2. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein A is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl.

3. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein A is phenyl or pyridyl.

4. The compound of formula (I) according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein

B is

(i) phenyl; and L^1 is –O–; or

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

5. The compound of formula (I) according to any one of claims 1-4, wherein:
m is 0, n is 0 and X is CR^8; or
m is 1, n is 1 and X is CR^8 or N.

6. The compound of formula (I) according to any one of claims 1-4, wherein m is 0, n is 0 and X is CR^8.

7. The compound of formula (I) according to any one of claims 1-6, wherein R^1 is hydrogen.

8. The compound of formula (I) according to any one of claims 1-7, wherein R^2 is hydrogen.

9. The compound of formula (I) according to any one of claims 1-8, wherein R^3 is hydrogen.

10. The compound of formula (I) according to any one of claims 1-9, wherein R^4 is hydrogen.

11. The compound of formula (I) according to any one of claims 1-10, wherein R^5 is hydrogen.

12. The compound of formula (I) according to any one of claims 1-11, wherein R^6 is selected from hydrogen, halogen, cyano, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkyl, C_{3-10}-cycloalkyl, and C_{1-6}-alkylsulfonyl.

13. The compound of formula (I) according to any one of claims 1-11, wherein R^6 is selected from hydrogen, halogen, cyano, and C_{1-6}-alkyl.

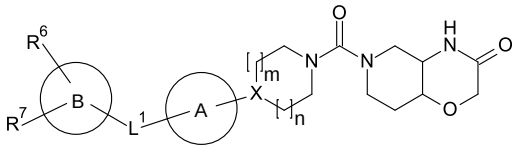
14. The compound of formula (I) according to any one of claims 1-11, wherein R^6 is selected from hydrogen, fluoro, chloro, cyano, methyl, and 2,2-dimethylpropyl.

15. The compound of formula (I) according to any one of claims 1-14, wherein R^7 is selected from hydrogen, halogen, and C_{1-6}-alkyl.

16. The compound of formula (I) according to any one of claims 1-14, wherein R^7 is selected from hydrogen, fluoro and methyl.

17. The compound of formula (I) according to any one of claims 1-16, wherein R^8 is hydrogen or hydroxy.

18. The compound of formula (I) according to claim 1, wherein the compound of formula (I) is a compound of formula (IIa), or a pharmaceutically acceptable salt thereof,



(IIa)

wherein:

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

B is

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

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

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

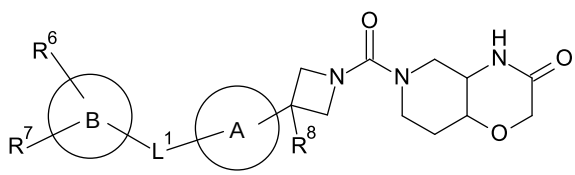
m is 1, n is 1 and X is CR^8 or N;

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

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

R^8 is selected from hydrogen and hydroxy.

19. The compound of formula (I) according to claim 1, wherein the compound of formula (I) is a compound of formula (IIb), or a pharmaceutically acceptable salt thereof,



(IIb)

wherein:

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

B is

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

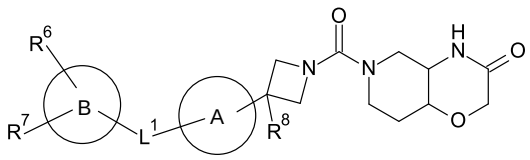
(ii) 5- to 14-membered heteroaryl; and L^1 is a covalent bond or –O–;

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

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

R^8 is selected from hydrogen and hydroxy.

20. The compound of formula (I) according to claim 1, wherein the compound of formula (I) is a compound of formula (IIb), or a pharmaceutically acceptable salt thereof,



(IIb)

wherein:

A is phenyl or pyridyl;

B is

(i) phenyl; and L^1 is –O–; or

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

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

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

R^8 is selected from hydrogen and hydroxy.

21. The compound of formula (I) according to any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, selected from:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2-[4-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]phenoxy]benzonitrile;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22. The compound of formula (I) according to any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, selected from:

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

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

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

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

2-[4-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]phenoxy]benzonitrile;

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

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

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

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

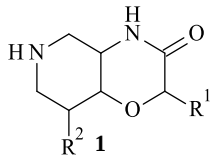
(4aR,8aS)-6-[3-[4-(3,6-dimethylpyridazin-4-yl)oxyphenyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

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

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

23. A process of manufacturing the compounds of formula (I) according to any one of claims 1 to 22, or pharmaceutically acceptable salts thereof, comprising:

reacting 4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-ones **1**, wherein R^1 and R^2 are as defined in any one of claims 1 to 22,



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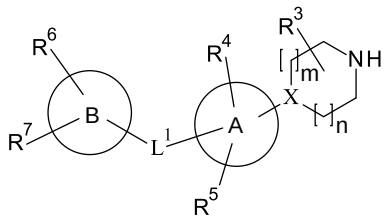
with a heterocyclic amine **2**, wherein A, B, L^1, X, m, n, and R^3 to R^7 are as defined in any one of claims 1 to 22



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in the presence of a base and a urea forming reagent,

to form said compounds of formula (I) or a pharmaceutically acceptable salt thereof.

~~24. A compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, when manufactured according to the process of claim 23.~~

~~25. A compound of formula (I) according to any one of claims 1 to 22 and 24, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) or~~

~~pharmaceutically acceptable salt thereof has an IC_{50} for monoacylglycerol lipase below 10 µM.~~

~~26.~~24. A compound of formula (I) according to any one of claims 1 to 22~~, 24 and 25~~, or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance.

~~27.~~25. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 22~~, 24 and 25~~, or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier.

~~28. The use of a compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 27 for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.~~

~~29. The use of a compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 27 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.~~

~~30.~~26. A compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim ~~27~~ 25 for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.

~~31.~~27. A compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim ~~27~~ 25 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.

~~32.~~28. The use of a compound of formula (I) according to any one of claims 1 to 22, 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.

~~33.~~29. The use of a compound of formula (I) according to any one of claims 1 to 22, 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.

~~34. 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 22, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 27 to the mammal.~~

~~35. 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 22, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 27 to the mammal.~~