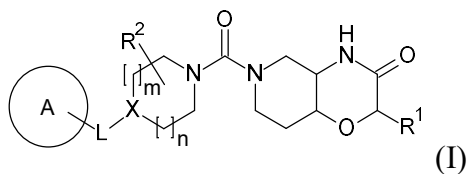


activation of MAGL is a promising new therapeutic strategy for providing neuroprotection and myelin regeneration. Accordingly, there is a high unmet medical need for new MAGL inhibitors.

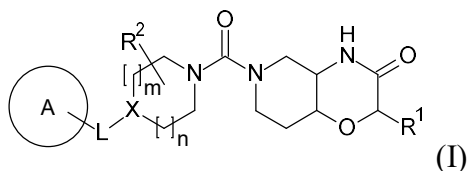
Summary

The present disclosure provides a compound of formula (I)



wherein A, L, X, m, n, R¹ and R² are as described herein.

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



or a pharmaceutically acceptable salt thereof,

wherein:

X is C-R³; m is 0 or 1; n is selected from 0, 1 and 2; and L is selected from -C≡C-, -CHR⁴-NR⁵-CH₂-, -NR⁵-CH₂-CHR⁴-, -NR⁵-CHR⁴-CH₂-, -CH₂-NR⁵-CHR⁴-, -(CR⁶R⁷)_p-C(O)-NR⁸-, -C(O)-NR⁸-(CR⁶R⁷)_p-, -(CR⁶R⁷)_p-NR⁸-C(O)-, -NR⁸-C(O)-(CR⁶R⁷)_p-, -(CH₂)_qNR⁹-, -NR⁹-(CH₂)_q-, -S-, -S(O)-, -SO₂-, -SCH₂-, -CH₂S-, -S(O)CH₂-, -CH₂S(O)-, -SO₂CH₂-, and -CH₂SO₂-; or

X is N; m is 1; n is 1 or 2; and L is selected from -NR⁵-CH₂-CHR⁴-, -NR⁵-CHR⁴-CH₂-, and -NR⁸-C(O)-(CR⁶R⁷)_p-;

p and q are each independently selected from 0, 1 and 2;

A is selected from:

- (i) C₆-C₁₄-aryl substituted with R¹⁰, R¹¹ and R¹²;
- (ii) 5- to 14-membered heteroaryl substituted with R¹³, R¹⁴ and R¹⁵; and
- (iii) 3- to 14-membered heterocycloalkyl substituted with R¹⁶, R¹⁷ and R¹⁸;
- (iv) C₃-C₁₀-cycloalkyl substituted with R²²;

R¹ is hydrogen or C₁₋₆-alkyl;

R² is selected from hydrogen, C₁₋₆-alkyl and hydroxy-C₁₋₆-alkyl;

R³ is selected from hydrogen, halogen, hydroxy, C₁₋₆-alkoxy, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

5 R⁴ is selected from hydrogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

R⁵ is selected from hydrogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl-CH₂-;

each of R⁶ and R⁷ is independently hydrogen or C₁₋₆-alkyl; or

R⁶ and R⁷, taken together with the carbon atom to which they are attached, form a 3- to 14-membered heterocycloalkyl or a C₃₋₁₀-cycloalkyl;

10 R⁸ is selected from hydrogen, C₁₋₆-alkyl, and hydroxy-C₁₋₆-alkyl;

R⁹ is selected from hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl-CH₂-, (C₁₋₆-alkyl)(halo-C₁₋₆-alkyl)CH- and hydroxy-C₁₋₆-alkyl-CH₂-;

each of R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ is independently selected from hydrogen, halogen, cyano, hydroxy, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, halo-C₁₋₆-alkyl-

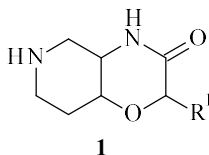
15 CH(OH)-, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, SF₅, C₁₋₆-alkylsulfonyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-cycloalkyl substituted with R¹⁹, 3- to 14-membered heterocycloalkyl, 3- to 14-membered heterocycloalkyl substituted with R²⁰, 5- to 14-membered heteroaryl, C₆-C₁₄-aryl and halo-C₆-C₁₄-aryl;

each of R¹⁹ and R²⁰ is independently selected from C₁₋₆-alkyl, cyano, and hydroxy; and

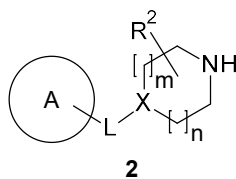
20 R²² is hydrogen or hydroxy.

The present disclosure provides a process of manufacturing the urea compounds of formula (I) described herein, comprising:

reacting a first amine of formula **1**, wherein R¹ is as described herein, preferably wherein R¹ is hydrogen,



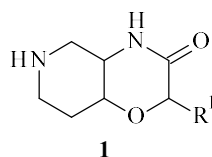
with a second amine **2**, wherein A, L, m, n, X and R² are as described herein



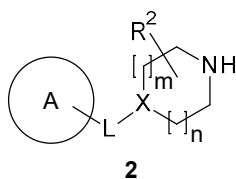
in the presence of a base and a urea forming reagent,
to form said compound of formula (I).

- 5 In another aspect, the present disclosure provides a process of manufacturing the compounds of formula (I) as described herein, comprising:

reacting a first amine of formula **1**, wherein R¹ is as described herein,



with a second amine **2**, wherein A, L, m, n, X and R² are as described herein



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

The present disclosure provides a compound of formula (I) as described herein, when manufactured according to the processes described herein.

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

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

The present disclosure 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.

The present 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 and/or mental disorders in a mammal.

The present 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 and/or spasticity associated with pain in a mammal.

The present disclosure provides a compound of formula (I) as described herein or a pharmaceutical composition described herein for use in a method of inhibiting monoacylglycerol lipase in a mammal.

In a further aspect, the present disclosure provides a compound of formula (I) as described herein or a pharmaceutical composition described herein 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 pharmaceutical composition 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 and/or spasticity associated with pain in a mammal.

The present disclosure provides the use of a compound of formula (I) as described herein for the preparation of a medicament for inhibiting monoacylglycerol lipase in a mammal.

The present disclosure provides the use of a compound of formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

- 5 In another aspect, the present disclosure provides the use of a compound of formula (I) as described herein or a pharmaceutical composition as described herein in the preparation of a medicament for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

- 10 The present disclosure provides the use of a compound 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 and/or spasticity associated with pain in a mammal.

- 15 In another aspect, the present disclosure provides the use of a compound of formula (I) as described herein or a pharmaceutical composition as described herein 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
20 cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal.

The present disclosure provides a method for inhibiting monoacylglycerol lipase in a mammal, which method comprises administering an effective amount of a compound of formula (I) as described herein or of a pharmaceutical composition described herein to the mammal.

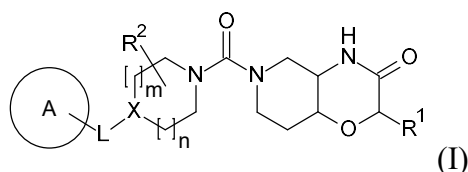
- 25 The present disclosure provides a method for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal, which method comprises administering an effective amount of a

compound of formula (I) as described herein or of a pharmaceutical composition described herein to the mammal.

- 5 The present disclosure provides a method for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, 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, which method comprises administering an effective amount of a compound of formula (I) as described herein or of a pharmaceutical composition described herein to the mammal.
- 10 The present disclosure also provides a method for determining the MAGL inhibitory activity of a test compound, e.g. of a compound of formula (I) described herein, comprising measuring the ratio of arachidonic acid / d8-arachidonic acid in a solution.

CLAIMS

1. A compound of formula (I)



or a pharmaceutically acceptable salt thereof,

wherein:

X is C-R³; m is 0 or 1; n is selected from 0, 1 and 2; and L is selected from -C≡C-, -CHR⁴-NR⁵-CH₂-, -NR⁵-CH₂-CHR⁴-, -NR⁵-CHR⁴-CH₂-, -CH₂-NR⁵-CHR⁴-, -(CR⁶R⁷)_p-C(O)-NR⁸-, -C(O)-NR⁸-(CR⁶R⁷)_p-, -(CR⁶R⁷)_p-NR⁸-C(O)-, -NR⁸-C(O)-(CR⁶R⁷)_p-, -(CH₂)_qNR⁹-, -NR⁹-(CH₂)_q-, -S-, -S(O)-, -SO₂-, -SCH₂-, -CH₂S-, -S(O)CH₂-, -CH₂S(O)-, -SO₂CH₂-, and -CH₂SO₂-; or

X is N; m is 1; n is 1 or 2; and L is selected from -NR⁵-CH₂-CHR⁴-, -NR⁵-CHR⁴-CH₂-, and -NR⁸-C(O)-(CR⁶R⁷)_p-;

p and q are each independently selected from 0, 1 and 2;

A is selected from:

- (i) C₆-C₁₄-aryl substituted with R¹⁰, R¹¹ and R¹²;
- (ii) 5- to 14-membered heteroaryl substituted with R¹³, R¹⁴ and R¹⁵; and
- (iii) 3- to 14-membered heterocycloalkyl substituted with R¹⁶, R¹⁷ and R¹⁸;
- (iv) C₃-C₁₀-cycloalkyl substituted with R²²;

R¹ is hydrogen or C₁₋₆-alkyl;

R² is selected from hydrogen, C₁₋₆-alkyl and hydroxy-C₁₋₆-alkyl;

R³ is selected from hydrogen, halogen, hydroxy, C₁₋₆-alkoxy, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

R⁴ is selected from hydrogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

R⁵ is selected from hydrogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl-CH₂-;

each of R⁶ and R⁷ is independently hydrogen or C₁₋₆-alkyl; or

R⁶ and R⁷, taken together with the carbon atom to which they are attached, form a 3- to 14-membered heterocycloalkyl or a C₃₋₁₀-cycloalkyl;

R⁸ is selected from hydrogen, C₁₋₆-alkyl, and hydroxy-C₁₋₆-alkyl;

R⁹ is selected from hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl-CH₂-, (C₁₋₆-alkyl)(halo-C₁₋₆-alkyl)CH- and hydroxy-C₁₋₆-alkyl-CH₂-;

- each of R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} is independently selected from hydrogen, halogen, cyano, hydroxy, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl, halo- C_{1-6} -alkyl-CH(OH)-, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, SF_5 , C_{1-6} -alkylsulfonyl, C_{3-10} -cycloalkyl, C_{3-10} -cycloalkyl substituted with R^{19} , 3- to 14-membered heterocycloalkyl, 3- to 14-membered heterocycloalkyl substituted with R^{20} , 5- to 14-membered heteroaryl, C_6 - C_{14} -aryl and halo- C_6 - C_{14} -aryl;
- each of R^{19} and R^{20} is independently selected from C_{1-6} -alkyl, cyano, and hydroxy; and
- 10 R^{22} is hydrogen or hydroxy.
2. The compound of formula I according to any one of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein:
- X is $C-R^3$;
- m, n and p are each independently 0 or 1;
- 15 L is selected from $-C\equiv C-$, $-CHR^4-NR^5-CH_2-$, $-CH_2-NR^5-CHR^4-$, $-(CR^6R^7)_p-C(O)-NR^8-$, $-(CR^6R^7)_p-NR^8-C(O)-$, $-(CH_2)_qNR^9-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SCH_2-$, $-CH_2S-$, $-S(O)CH_2-$, $-CH_2S(O)-$, $-SO_2CH_2-$, and $-CH_2SO_2-$;
- q is 0;
- R^2 is hydrogen;
- 20 R^3 is selected from hydrogen, hydroxy, and C_{1-6} -alkyl;
- R^4 is halo- C_{1-6} -alkyl;
- R^6 and R^7 are both hydrogen; or
- R^6 and R^7 , together with the carbon atom to which they are attached, form a C_{3-10} -cycloalkyl; and
- 25 R^9 is C_{1-6} -alkyl.
3. The compound of formula I according to claim 2, or a pharmaceutically acceptable salt thereof, wherein:
- X is $C-R^3$;
- m and n are both 0; or
- 30 m and n are both 1;
- q is 0;

L is selected from $-\text{C}\equiv\text{C}-$, $-\text{CHR}^4-\text{NR}^5-\text{CH}_2-$, $-(\text{CH}_2)_q\text{NR}^9-$, $-\text{SCH}_2-$, and $-\text{CH}_2\text{S}-$

R^2 , R^3 and R^5 are all hydrogen;

R^4 is halo- C_{1-6} -alkyl; and

R^9 is C_{1-6} -alkyl.

- 5 4. The compound of formula I according to claim 3, or a pharmaceutically acceptable salt thereof, wherein:

X is $\text{C}-\text{R}^3$;

m and n are both 0; or

m and n are both 1;

10 q is 0;

L is selected from $-\text{C}\equiv\text{C}-$, $-\text{CHR}^4-\text{NR}^5-\text{CH}_2-$, $-(\text{CH}_2)_q\text{NR}^9-$, $-\text{SCH}_2-$, and $-\text{CH}_2\text{S}-$

R^2 , R^3 and R^5 are all hydrogen;

R^4 is CF_3 ; and

R^9 is methyl.

- 15 5. The compound of formula I according to any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein A is selected from:

(i) $\text{C}_6\text{-C}_{14}$ -aryl substituted with R^{10} , R^{11} and R^{12} ;

(ii) 5- to 14-membered heteroaryl substituted with R^{13} , R^{14} and R^{15} ; and

(iii) $\text{C}_3\text{-C}_{10}$ -cycloalkyl substituted with R^{22} ;

20 wherein:

R^{10} is selected from hydrogen, C_{1-6} -alkyl, C_{1-6} -alkylsulfonyl, C_{1-6} -alkoxy, halo- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl, C_{3-10} -cycloalkyl, C_{3-10} -cycloalkyl substituted with R^{19} , cyano, and halogen;

R^{11} is selected from hydrogen, C_{1-6} -alkyl, and halogen;

25 R^{12} is hydrogen or halogen;

R^{13} is halogen;

R^{14} and R^{15} are both hydrogen;

R^{19} is hydroxy or cyano; and

R^{22} is hydrogen or hydroxy.

- 30 6. The compound of formula I according to any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

A is $\text{C}_6\text{-C}_{14}$ -aryl substituted with R^{10} , R^{11} and R^{12} ;

R¹⁰ is selected from C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, C₃₋₁₀-cycloalkyl, and halogen;

R¹¹ is selected from hydrogen, C₁₋₆-alkyl, and halogen; and

R¹² is hydrogen or halogen.

- 5 7. The compound of formula I according to any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

A is phenyl substituted with R¹⁰, R¹¹ and R¹²;

R¹⁰ is methyl, difluoromethyl, CF₃, OCF₃, cyclopropyl, fluoro, or chloro;

R¹¹ is hydrogen, methyl, chloro, or fluoro; and

10 R¹² is hydrogen or fluoro.

8. The compound of formula I according to any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen.

9. A compound of formula (I) according to any one of claims 1 to 8, selected from:

- (4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)phenyl)thio)azetidine-1-
15 carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
(4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)phenyl)sulfonyl)azetidine-1-
carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
(4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)phenyl)sulfinyl)azetidine-1-
carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
20 (4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)phenyl)sulfinyl)azetidine-1-
carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
(4aR,8aS)-6-(3-(((2-Chloro-4-(trifluoromethyl)phenyl)thio)methyl)azetidine-1-
carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
(4aR,8aS)-6-(3-((2-Fluoro-6-(trifluoromethyl)benzyl)sulfonyl)azetidine-1-
25 carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
(4aR,8aS)-6-[3-[[2-Fluoro-6-(trifluoromethyl)phenyl]methylsulfinyl]azetidine-1-
carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
(4aR,8aS)-6-(3-(((2-Chloro-4-(trifluoromethyl)phenyl)sulfonyl)methyl)azetidine-1-
carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
30 (4aR,8aS)-6-(3-(((2-Chloro-4-(trifluoromethyl)phenyl)sulfinyl)methyl)azetidine-1-
carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;

- (4aR,8aS)-6-(3-((2-Fluoro-4-(trifluoromethyl)benzyl)thio)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-((2,6-Dichlorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 5 (4aR,8aS)-6-[3-[2-[2-Fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-(3-((2,6-Difluorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-((3-Chloro-4-(trifluoromethyl)phenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 10 (4aR,8aS)-6-(3-((2-Chloro-6-fluorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-((2-Chloro-4-cyclopropylphenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 15 (4aR,8aS)-6-(3-((2-Methoxyphenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-[4-Chloro-2-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(3-Chlorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 20 (4aR,8aS)-6-[3-[2-[4-Trifluoromethoxy]phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[4-(Trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 25 (4aR,8aS)-6-[3-[2-(3-Fluoro-2-methylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(2,6-Dimethylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-(Trifluoromethoxy)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 30 (4aR,8aS)-6-[3-[2-(2-Bromophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-(3-((2-Chloro-3-fluorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;

- (4aR,8aS)-6-(3-(o-Tolylethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-(4-Chloro-2-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 5 (4aR,8aS)-6-[3-[2-[2-(Difluoromethoxy)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 2-[2-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]ethynyl]-3-chlorobenzonitrile;
- (4aR,8aS)-6-[3-[2-[4-(Difluoromethoxy)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 10 1-[4-[2-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]ethynyl]phenyl]cyclopropane-1-carbonitrile;
- (4aR,8aS)-6-[3-[2-(4-Cyclopropylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 15 (4aR,8aS)-6-[3-[2-[4-(1-Hydroxycyclopropyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(3-Methoxyphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-(Difluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 20 (4aR,8aS)-6-[3-[2-(3-Methoxy-2-methylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(2-Chloro-6-methylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 25 (4aR,8aS)-6-[3-[2-(2-Chloro-5-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(4-Methylsulfonylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(5-Chlorothiophen-2-yl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 30 (4aR,8aS)-6-[3-[2-(5-Chlorothiophen-3-yl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-Chloro-6-fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

- (4aR,8aS)-6-[3-[2-(2-Chlorophenyl)ethynyl]-3-hydroxyazetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-(Methoxymethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 5 (4aR,8aS)-6-(4-((2-(Trifluoromethyl)phenyl)ethynyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(4-((2-Methoxyphenyl)ethynyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(4-(o-Tolyethynyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 10 (4aR,8aS)-6-(4-((2,6-Dimethylphenyl)ethynyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(4-((2,4-Dichlorophenyl)ethynyl)-4-methylpiperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 15 (4aR,8aS)-6-(4-((2-Chloro-4-fluorophenyl)ethynyl)-4-methylpiperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-(1-Hydroxycyclopentyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(Cyclopenten-1-yl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 20 (4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)phenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-((2-Fluoro-6-(trifluoromethyl)benzyl)thio)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 25 (+)- or (-)-(4aR,8aS)-6-[3-[[[2,2,2-Trifluoro-1-[4-(trifluoromethyl)phenyl]ethyl]amino]methyl]azetidine-1-carbonyl]hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (+)- or (-)-N-Benzyl-N-(2-hydroxyethyl)-1-((4aR,8aS)-3-oxooctahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carbonyl)piperidine-4-carboxamide;
- 30 (+)- or (-)-N-Benzyl-1-((4aR,8aS)-3-oxooctahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carbonyl)piperidine-4-carboxamide;
- (+)- or (-)-(4aR,8aS)-6-(3-(((2,2,2-Trifluoro-1-(3-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;

- (+)- or (-)-(4aR,8aS)-6-(3-(((1-(2,4-Dichlorophenyl)-2,2,2-trifluoroethyl)amino)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 5 (+)- or (-)-(4aR,8aS)-6-(3-(((1-(2-Chlorophenyl)-2,2,2-trifluoroethyl)amino)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (+)- or (-)-(4aR,8aS)-6-(3-(((2,2,2-Trifluoro-1-phenylethyl)amino)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 10 (+)- or (-)-2-Chloro-4-fluoro-N-(1-((4aR,8aS)-3-oxooctahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carbonyl)azetidin-3-yl)benzamide;
- (+)- or (-)-(4aR,8aS)-6-(3-((Methyl(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 15 N-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]-N-methyl-1-[3-(trifluoromethyl)phenyl]cyclopropane-1-carboxamide;
- N-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]-2-[2-chloro-3-(trifluoromethyl)phenyl]-N-methylacetamide;
- 20 N-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]-2-[2-chloro-5-(trifluoromethyl)phenyl]-N-methylacetamide;
- N-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]-N-methyl-4-(trifluoromethyl)benzamide;
- 25 N-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]-N-methyl-2-[3-(trifluoromethyl)phenyl]acetamide;
- (4aR,8aS)-6-[3-[[[2,2,2-Trifluoro-1-(4-fluorophenyl)ethyl]amino]methyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[4-[2,2,2-Trifluoro-1-[[3-(trifluoromethyl)phenyl]methylamino]ethyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 30 (4aR,8aS)-6-[4-[2-(2-Chlorophenyl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

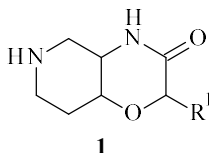
- (4aR,8aS)-6-[4-[2-(4-Chloropyridin-3-yl)ethynyl]piperidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (+)- or (-)-(4aR,8aS)-6-[4-[2-(3-Chloropyridin-2-yl)ethynyl]piperidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 5 (+)- or (-)-(4aR,8aS)-6-[4-[2-(2-Chloro-4-fluorophenyl)ethynyl]piperidine-1-
carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (+)- or (-)-(4aR,8aS)-6-(4-((3-Chlorophenyl)ethynyl)piperidine-1-
carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (+)- or (-)-(4aR,8aS)-6-(4-((4-Chlorophenyl)ethynyl)piperidine-1-
10 carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (+)- or (-)-(4aR,8aS)-6-(4-((2,4-Dichlorophenyl)ethynyl)piperidine-1-
carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (+)- or (-)-(4aR,8aS)-6-[4-[2-(2-Chlorophenyl)ethynyl]-4-hydroxypiperidine-1-
carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 15 (4aR,8aS)-6-[3-[2-(2-Chlorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-(3-((2,4-Dichlorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-
pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-(2-Chloro-4-fluorophenyl)ethynyl]azetidine-1-carbonyl]-
20 4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[4-[N-methyl-4-(trifluoromethyl)anilino]piperidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and
- (4aR,8aS)-6-[3-[N-methyl-4-(trifluoromethyl)anilino]azetidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one.
- 25 10. A compound of formula (I) according to any one of claims 1 to 8, selected from:
- (+)- or (-)-(4aR,8aS)-6-[3-[[[2,2,2-Trifluoro-1-[4-
(trifluoromethyl)phenyl]ethyl]amino]methyl]azetidine-1-carbonyl]hexahydro-
2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[4-[2-(2-Chlorophenyl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-
30 hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (+)- or (-)-(4aR,8aS)-6-[4-[2-(2-Chloro-4-fluorophenyl)ethynyl]piperidine-1-
carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

- (4aR,8aS)-6-[3-[2-(2-Chlorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(2-Chloro-4-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 5 (4aR,8aS)-6-[4-[N-methyl-4-(trifluoromethyl)anilino]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-(3-(((2-Chloro-4-(trifluoromethyl)phenyl)thio)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-((2-Fluoro-4-(trifluoromethyl)benzyl)thio)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 10 (4aR,8aS)-6-(3-((2,6-Dichlorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-[2-Fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 15 (4aR,8aS)-6-(3-((2-Chloro-6-fluorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-((2-Chloro-4-cyclopropylphenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-[4-Trifluoromethoxy]phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 20 (4aR,8aS)-6-[3-[2-(2,6-Dimethylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-(Trifluoromethoxy)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 25 (4aR,8aS)-6-(3-(o-Tolyethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-(4-Chloro-2-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-(Difluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 30 (4aR,8aS)-6-[3-[2-(2-Chloro-6-methylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-Chloro-6-fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and

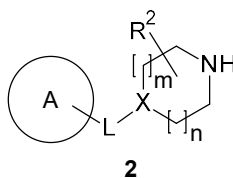
(4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)phenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one.

11. A process of manufacturing the compounds of formula (I) according to any one of claims 1 to 10, comprising:

5 reacting a first amine of formula **1**, wherein R¹ is as described in any one of claims 1 to 10,



with a second amine **2**, wherein A, L, m, n, X and R² are as described in any one of claims 1 to 10



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

12. A compound of formula (I) according to any one of claims 1 to 10 for use as therapeutically active substance.

15 13. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 10 and a therapeutically inert carrier.

14. A compound of formula (I) according to any one of claims 1 to 10 or a pharmaceutical composition according to claim 13 for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or
20 mental disorders in a mammal.

15. A compound of formula (I) according to any one of claims 1 to 10 or a pharmaceutical composition according to claim 13 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,
25 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.

16. The use of a compound of formula (I) according to any one of claims 1 to 10 or a pharmaceutical composition according to claim 13 in the preparation of a medicament for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.
17. The use of a compound of formula (I) according to any one of claims 1 to 10 or a pharmaceutical composition according to claim 13 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 and/or spasticity associated with pain in a mammal.