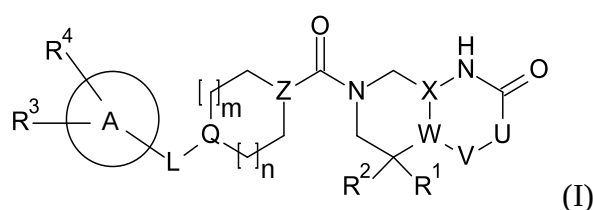


are driven mainly via cannabinoid receptors (CBRs), CB1 and CB2. CB1 receptors are present throughout the GI tract of animals and healthy humans, especially in the enteric nervous system (ENS) and the epithelial lining, as well as smooth muscle cells of blood vessels in the colonic wall (Wright K. *et al.*, *Gastroenterology* **2005**, 129(2), 437-453; Duncan, M. *et al.*, *Aliment Pharmacol Ther* **2005**, 22(8), 667-683). Activation of CB1 produces anti-emetic, anti-motility, and anti-inflammatory effect, and help to modulate pain (Perisetti, A. *et al.*, *Ann Gastroenterol* **2020**, 33(2), 134-144). CB2 receptors are expressed in immune cells such as plasma cells and macrophages, in the lamina propria of the GI tract (Wright K. *et al.*, *Gastroenterology* **2005**, 129(2), 437-453), and primarily on the epithelium of human colonic tissue associated with inflammatory bowel disease (IBD). Activation of CB2 exerts anti-inflammatory effect by reducing pro-inflammatory cytokines. Expression of MAGL is increased in colonic tissue in UC patients (Marquez L. *et al.*, *PLoS One* **2009**, 4(9), e6893) and 2-AG levels are increased in plasma of IBD patients (Grill, M. *et al.*, *Sci Rep* **2019**, 9(1), 2358). Several animal studies have demonstrated the potential of MAGL inhibitors for symptomatic treatment of IBD. MAGL inhibition prevents TNBS-induced mouse colitis and decreases local and circulating inflammatory markers via a CB1/CB2 MoA (Marquez L. *et al.*, *PLoS One* **2009**, 4(9), e6893). Furthermore, MAGL inhibition improves gut wall integrity and intestinal permeability via a CB1 driven MoA (Wang, J. *et al.*, *Biochem Biophys Res Commun* **2020**, 525(4), 962-967).

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

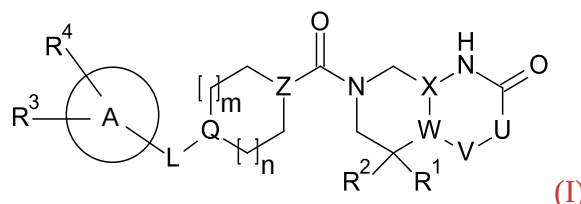
Summary of the Invention

In a first aspect, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof,



wherein A, L, Q, U, V, W, X, Z, m, n, and R¹ to R⁴ are as described herein.

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



or a pharmaceutically acceptable salt thereof,

wherein:

(i) U is CH₂;

V is O;

W and X are both CH;

R¹ is selected from halogen and C₁₋₆-alkyl; and

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

R¹ and R², taken together with the carbon atom to which they are attached, form a C₃-C₁₀-cycloalkyl; or

(ii) U is CH₂;

V is O;

W is CR^w;

X is CH;

R^w is selected from halogen, and C₁₋₆-alkyl;

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

R¹ and R², taken together with the carbon atom to which they are attached, form a C₃-C₁₀-cycloalkyl; or

(iii) U is CH₂;

V is O;

W and X together form a group C=C; and

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

R¹ and R², taken together with the carbon atom to which they are attached, form a C₃-C₁₀-cycloalkyl; or

(iv) U is CH₂;

V is selected from NH, CH₂, S, S=O, SO₂, CHOH, CHF, and CF₂;

(a) W is CR^w; and

X is CH; or

(b) W and X together form a group C=C;

R^w is selected from hydrogen, halogen, and C₁₋₆-alkyl;

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

R¹ and R², taken together with the carbon atom to which they are attached, form a C₃-C₁₀-cycloalkyl; or

(v) U and V together form a group C=C;

W and X together form a group C=C; and

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

R¹ and R², taken together with the carbon atom to which they are attached, form a C₃-C₁₀-cycloalkyl; or

(vi) U is CH₂;

V is O;

W is CH;

X is C-OH; and

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

R¹ and R², taken together with the carbon atom to which they are attached, form a C₃-C₁₀-cycloalkyl;

m and n are both 0; or

m and n are both 1;

Z is CH or N;

Q is CR^q or N;

R^q is selected from hydrogen, halogen, hydroxy, halo-C₁₋₆-alkyl, and C₁₋₆-alkyl.

L is selected from a covalent bond, -CHR⁵-, -O-, -OCH₂-, -CH₂O-, -CH₂OCH₂-, -CF₂CH₂-, and -CH₂CF₂-;

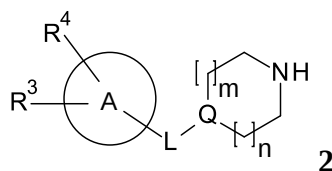
A is selected from C₆-C₁₄-aryl, 5- to 14-membered heteroaryl, and 3- to 14-membered heterocyclyl;

R³ and R⁴ are independently selected from hydrogen, halogen, SF₅, cyano, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, C₆-C₁₄-aryl, C₃-C₁₀-cycloalkyl, 5-14-membered heteroaryl, C₆-C₁₄-aryloxy, C₃-C₁₀-cycloalkyloxy, and 5-14-membered heteroaryloxy, wherein said C₆-C₁₄-aryl, C₃-C₁₀-cycloalkyl, 5-14-membered heteroaryl, C₆-C₁₄-aryloxy, C₃-C₁₀-cycloalkyloxy, and 5-14-membered heteroaryloxy, are optionally substituted with 1-2 substituents selected from halogen, C₁₋₆-alkyl, and halo-C₁₋₆-alkyl; and

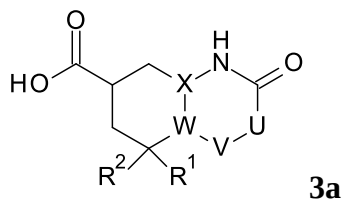
R⁵ is selected from hydrogen and C₆-C₁₄-aryl.

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

- (a) reacting an amine of formula **2**, wherein m, n, Q, L, A, R³ and R⁴ are as described herein,

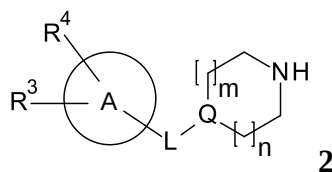


with a carboxylic acid **3a**, wherein U, V, W, X, R¹ and R² are as described herein

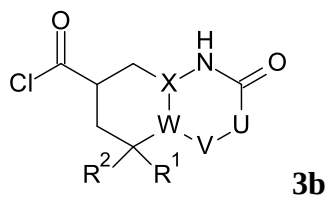


in the presence of a coupling reagent, and optionally in the presence of a base; or

- (b) reacting an amine of formula **2**, wherein m, n, Q, L, A, R³ and R⁴ are as described herein,

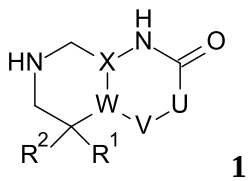


with a carboxylic acid chloride **3b**, wherein U, V, W, X, R¹ and R² are as described herein

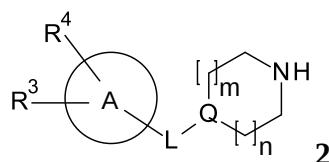


in the presence of a base; or

- (c) reacting a first amine of formula **1**, wherein U, V, W, X, R¹ and R² are as described herein,



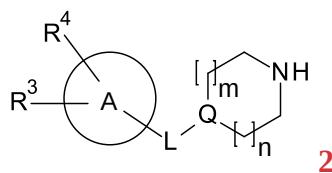
with a second amine **2**, wherein A, L, m, n, Q, R³ and R⁴ are as described herein



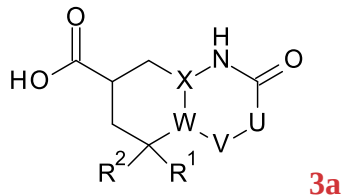
in the presence of a base and a urea forming reagent,
to form said compound of formula (I).

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

(a) reacting an amine of formula **2**, wherein m, n, Q, L, A, R³ and R⁴ are as described herein,

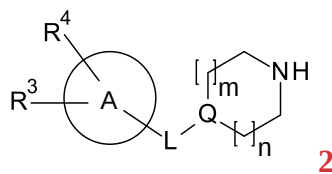


10 with a carboxylic acid **3a**, wherein U, V, W, X, R¹ and R² are as described herein



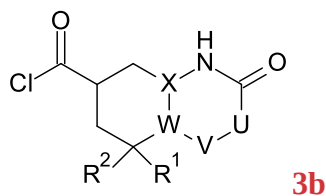
in the presence of a coupling reagent, and optionally in the presence of a base; or

(b) reacting an amine of formula **2**, wherein m, n, Q, L, A, R³ and R⁴ are as described herein,



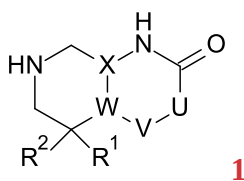
15 with a carboxylic acid chloride **3b**, wherein U, V, W, X, R¹ and R² are as described herein

- 6a -

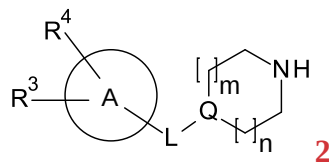


in the presence of a base; or

(c) reacting a first amine of formula 1, wherein U, V, W, X, R¹ and R² are as described herein,



with a second amine 2, wherein A, L, m, n, Q, R³ and R⁴ are as described herein



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

to form said compound of formula (I).

In a further aspect, the~~The~~ present ~~invention~~disclosure provides a compound of formula (I) 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 (I) as described herein, for use as therapeutically active substance. In another aspect, the present 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~~The~~ present ~~invention~~disclosure provides a pharmaceutical composition comprising a compound of formula (I) as described herein and a therapeutically inert carrier. In another aspect, the present 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 the use of a compound of formula (I) as described herein or of a pharmaceutical composition described herein for inhibiting monoacylglycerol lipase (MAGL) in a mammal.

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

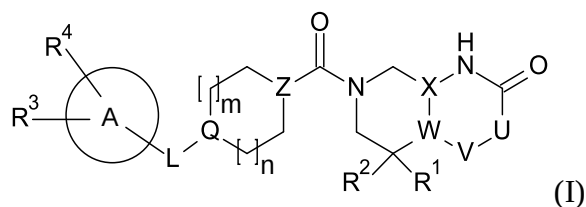
In another aspect, the present disclosure provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as described herein for use in the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, 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.

- 5 In another 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,
- 10 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.

CLAIMS

1. A compound of formula (I)



or a pharmaceutically acceptable salt thereof,

wherein:

- (i) U is CH₂;

V is O;

W and X are both CH;

R¹ is selected from halogen and C₁₋₆-alkyl; and

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

R¹ and R², taken together with the carbon atom to which they are attached, form a C₃-C₁₀-cycloalkyl; or

- (ii) U is CH₂;

V is O;

W is CR^w;

X is CH;

R^w is selected from halogen, and C₁₋₆-alkyl;

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

or

R¹ and R², taken together with the carbon atom to which they are attached, form a C₃-C₁₀-cycloalkyl; or

- (iii) U is CH₂;

V is O;

W and X together form a group C=C; and

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

or

R¹ and R², taken together with the carbon atom to which they are attached, form a C₃-C₁₀-cycloalkyl; or

- (iv) U is CH₂;

V is selected from NH, CH₂, S, S=O, SO₂, CHOH, CHF, and CF₂;

- (a) W is CR^w; and
X is CH; or
- (b) W and X together form a group C=C;
R^w is selected from hydrogen, halogen, and C₁₋₆-alkyl;
5 R¹ and R² are independently selected from hydrogen, halogen, and C₁₋₆-alkyl;
or
R¹ and R², taken together with the carbon atom to which they are attached,
form a C₃-C₁₀-cycloalkyl; or
- (v) U and V together form a group C=C;
10 W and X together form a group C=C; and
R¹ and R² are independently selected from hydrogen, halogen, and C₁₋₆-alkyl;
or
R¹ and R², taken together with the carbon atom to which they are attached,
form a C₃-C₁₀-cycloalkyl; or
- (vi) 15 U is CH₂;
V is O;
W is CH;
X is C-OH; and
R¹ and R² are independently selected from hydrogen, halogen, and C₁₋₆-alkyl;
20 or
R¹ and R², taken together with the carbon atom to which they are attached,
form a C₃-C₁₀-cycloalkyl;
- m and n are both 0; or
m and n are both 1;
- 25 Z is CH or N;
Q is CR^q or N;
R^q is selected from hydrogen, halogen, hydroxy, halo-C₁₋₆-alkyl, and C₁₋₆-alkyl.
L is selected from a covalent bond, -CHR⁵-, -O-, -OCH₂-, -CH₂O-, -CH₂OCH₂-,
-CF₂CH₂-, and -CH₂CF₂-;
- 30 A is selected from C₆-C₁₄-aryl, 5- to 14-membered heteroaryl, and 3- to 14-
membered heterocyclyl;
R³ and R⁴ are independently selected from hydrogen, halogen, SF₅, cyano, C₁₋₆-
alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, C₆-C₁₄-aryl, C₃-C₁₀-
cycloalkyl, 5-14-membered heteroaryl, C₆-C₁₄-aryloxy, C₃-C₁₀-cycloalkyloxy,

and 5-14-membered heteroaryloxy, wherein said C₆-C₁₄-aryl, C₃-C₁₀-cycloalkyl, 5-14-membered heteroaryl, C₆-C₁₄-aryloxy, C₃-C₁₀-cycloalkyloxy, and 5-14-membered heteroaryloxy, are optionally substituted with 1-2 substituents selected from halogen, C₁₋₆-alkyl, and halo-C₁₋₆-alkyl; and

5 R⁵ is selected from hydrogen and C₆-C₁₄-aryl.

2. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(i) U is CH₂;

V is O;

10 W and X are both CH;

R¹ is selected from halogen and C₁₋₆-alkyl; and

R² is selected from hydrogen and halogen; or

(ii) U is CH₂;

V is O;

15 W and X together form a group C=C; and

R¹ and R² are both hydrogen; or

(iii) U is CH₂;

V is selected from NH, S, and CH₂;

(a) W and X are both CH; or

20 (b) W and X together form a group C=C; and

R¹ and R² are both hydrogen;

(iv) U and V together form a group C=C;

W and X together form a group C=C; and

R¹ and R² are both hydrogen; or

25 (v) U is CH₂;

V is O;

W is CH;

X is C-OH; and

R¹ and R² are both hydrogen.

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

(i) U is CH₂;

V is O;

- W and X are both CH;
R¹ is selected from halogen and C₁₋₆-alkyl; and
R² is selected from hydrogen and halogen; or
- (ii) U is CH₂;
5 V is NH;
W and X are both CH; and
R¹ and R² are both hydrogen; or
- (iii) U and V together form a group C=C;
W and X together form a group C=C; and
10 R¹ and R² are both hydrogen.
4. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein
- (i) U is CH₂;
V is O;
15 W and X are both CH;
R¹ is selected from fluoro and methyl; and
R² is selected from hydrogen and fluoro; or
- (ii) U is CH₂;
V is NH;
20 W and X are both CH; and
R¹ and R² are both hydrogen; or
- (iii) U and V together form a group C=C;
W and X together form a group C=C; and
R¹ and R² are both hydrogen.
- 25 5. The compound of formula I according to any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein Z is N.
6. The compound of formula I according to any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein Q is CH.
7. The compound of formula I according to any one of claims 1-6, or a
30 pharmaceutically acceptable salt thereof, wherein m and n are both 0.

8. The compound of formula I according to any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein L is selected from a covalent bond, $-\text{CHR}^5-$, and $-\text{CH}_2\text{O}-$.
9. The compound of formula I according to any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein L is selected from a covalent bond and $-\text{CH}_2\text{O}-$.
10. The compound of formula I according to any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein A is $\text{C}_6\text{-C}_{14}$ -aryl.
11. The compound of formula I according to any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein A is phenyl.
12. The compound of formula I according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from hydrogen and halo- $\text{C}_1\text{-C}_6$ -alkyl.
13. The compound of formula I according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^3 is halo- $\text{C}_1\text{-C}_6$ -alkyl.
14. The compound of formula I according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from CF_3 and 2,2,2-trifluoroethyl.
15. The compound of formula I according to any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen and halogen.
16. The compound of formula I according to any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen and fluoro.
17. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:
 - (i) U is CH_2 ;
V is O;
W and X are both CH;
 R^1 is selected from halogen and C_{1-6} -alkyl; and

R^2 is selected from hydrogen and halogen; or

(ii) U is CH_2 ;

V is O;

W and X together form a group $C=C$; and

5 R^1 and R^2 are both hydrogen; or

(iii) U is CH_2 ;

V is selected from NH, S, and CH_2 ;

(a) W and X are both CH; or

(b) W and X together form a group $C=C$; and

10 R^1 and R^2 are both hydrogen;

(iv) U and V together form a group $C=C$;

W and X together form a group $C=C$; and

R^1 and R^2 are both hydrogen; or

(v) U is CH_2 ;

15 V is O;

W is CH;

X is C-OH; and

R^1 and R^2 are both hydrogen;

Z is N;

20 Q is CH;

m and n are both 0;

L is selected from a covalent bond, $-CHR^5-$, and $-CH_2O-$;

A is C_6-C_{14} -aryl;

R^3 is selected from hydrogen and halo- C_1-C_6 -alkyl;

25 R^4 is selected from hydrogen and halogen; and

R^5 is selected from hydrogen and C_6-C_{14} -aryl.

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

(i) U is CH_2 ;

30 V is O;

W and X are both CH;

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

R^2 is selected from hydrogen and halogen; or

(ii) U is CH_2 ;

V is NH;

W and X are both CH; and

R¹ and R² are both hydrogen; or

(iii) U and V together form a group C=C;

5 W and X together form a group C=C; and

R¹ and R² are both hydrogen;

Z is N;

Q is CH;

m and n are both 0;

10 L is selected from a covalent bond and -CH₂O-;

A is C₆-C₁₄-aryl;

R³ is halo-C₁-C₆-alkyl; and

R⁴ is selected from hydrogen and halogen.

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

(i) U is CH₂;

V is O;

W and X are both CH;

R¹ is selected from fluoro and methyl; and

20 R² is selected from hydrogen and fluoro; or

(ii) U is CH₂;

V is NH;

W and X are both CH; and

R¹ and R² are both hydrogen; or

25 (iii) U and V together form a group C=C;

W and X together form a group C=C; and

R¹ and R² are both hydrogen;

Z is N;

Q is CH;

30 m and n are both 0;

L is selected from a covalent bond and -CH₂O-;

A is phenyl;

R³ is selected from CF₃ and 2,2,2-trifluoroethyl; and

R⁴ is selected from hydrogen and fluoro.

20. A compound of formula (I) according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, selected from:

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

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

rel-(4aS,8aS)-8,8-Difluoro-6-[3-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4a,5,7,8a-tetrahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one;

10 rel-(4aR,8aR)-8,8-Difluoro-6-[3-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4a,5,7,8a-tetrahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one;

rel-(4aS,8aS)-8,8-Difluoro-6-[3-[4-(2,2,2-trifluoroethyl)phenyl]azetidine-1-carbonyl]-4a,5,7,8a-tetrahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one;

15 rel-(4aR,8aR)-8,8-Difluoro-6-[3-[4-(2,2,2-trifluoroethyl)phenyl]azetidine-1-carbonyl]-4a,5,7,8a-tetrahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one;

6-[4-[[4-(Trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,5,7,8-tetrahydropyrido[4,3-b][1,4]oxazin-3-one;

7-(4-Benzhydrylpiperidine-1-carbonyl)-1,5,6,8-tetrahydro-1,7-naphthyridin-2-one;

20 7-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-1,5,6,8-tetrahydro-1,7-naphthyridin-2-one;

rac-(4aS,8aS)-7-(4-Benzhydrylpiperidine-1-carbonyl)-1,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-2-one;

rac-(4aS,8aS)-7-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-1,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-2-one;

25 rac-(4aR,8aS)-6-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-1,2,4,4a,5,7,8,8a-octahydropyrido[3,4-b]pyrazin-3-one;

(4aR,8aS)-or (4aS,8aR)-6-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-1,2,4,4a,5,7,8,8a-octahydropyrido[3,4-b]pyrazin-3-one;

30 (4aS,8aR)- or (4aR,8aS)-6-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-1,2,4,4a,5,7,8,8a-octahydropyrido[3,4-b]pyrazin-3-one; and

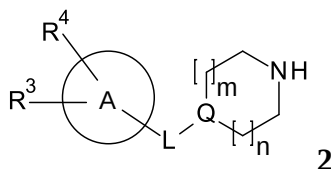
6-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-
1,2,4,5,7,8-hexahydropyrido[3,4-b]pyrazin-3-one.

21. A compound of formula (I) according to any one of claims 1 to 19, or a
pharmaceutically acceptable salt thereof, selected from:

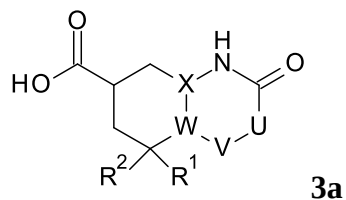
- 5 (4aS,8aS)- or (4aR,8aR)-8,8-Difluoro-6-[3-[4-(2,2,2-trifluoroethyl)phenyl]azetidine-
1-carbonyl]-4a,5,7,8a-tetrahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one;
rac-(4aR,8aR)-8,8-Difluoro-6-[3-[[2-fluoro-4-
(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4a,5,7,8a-tetrahydro-4H-
pyrido[4,3-b][1,4]oxazin-3-one;
- 10 (4aR,8S,8aS)- or (4aR,8R,8aS)-6-[3-[[2-Fluoro-4-
(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-8-methyl-4,4a,5,7,8,8a-
hexahydropyrido[4,3-b][1,4]oxazin-3-one;
7-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-1,5,6,8-
tetrahydro-1,7-naphthyridin-2-one;
- 15 rac-(4aR,8aS)-6-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-
carbonyl]-1,2,4,4a,5,7,8,8a-octahydropyrido[3,4-b]pyrazin-3-one;
(4aS,8aS)-6-[3-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-
4a-hydroxy-5,7,8,8a-tetrahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one;
rac-(4aS,8aS)-7-[3-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-
20 carbonyl]-4-hydroxy-1,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-2-one; and
6-[3-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,5,7,8-
tetrahydropyrido[4,3-b][1,4]thiazin-3-one.

22. A process of manufacturing the compounds of formula (I) according to any one of
claims 1 to 21, or pharmaceutically acceptable salts thereof, comprising:

- 25 (a) reacting an amine of formula **2**, wherein m, n, Q, L, A, R³ and R⁴ are as
defined in any one of claims 1 to 21,

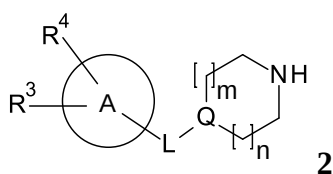


with a carboxylic acid **3a**, wherein U, V, W, X, R¹ and R² are as defined in any
one of claim 1 to 21

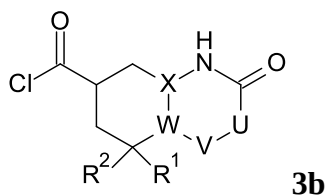


in the presence of a coupling reagent, and optionally in the presence of a base;
or

- (b) reacting an amine of formula **2**, wherein m, n, Q, L, A, R³ and R⁴ are as defined in any one of claims 1 to 21,

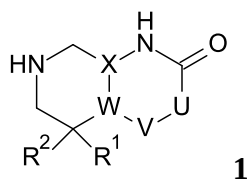


with a carboxylic acid chloride **3b**, wherein U, V, W, X, R¹ and R² are as defined in any one of claims 1 to 21

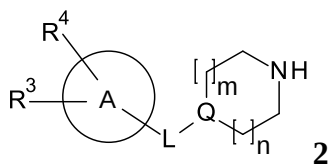


in the presence of a base; or

- (c) reacting a first amine of formula **1**, wherein U, V, W, X, R¹ and R² are as defined in any one of claims 1 to 21,



with a second amine **2**, wherein A, L, m, n, Q, R³ and R⁴ are as defined in any one of claims 1 to 21



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

~~23. A compound of formula (I) according to any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, when manufactured according to the process of claim 22.~~

24.23. A compound of formula (I) according to any one of claims 1 to 21 ~~and 23~~, or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance.

25.24. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 21 ~~and 23~~, or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier.

~~26. The use of a compound of formula (I) according to any one of claims 1 to 21 and 23, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 25 for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.~~

~~27. The use of a compound of formula (I) according to any one of claims 1 to 21 and 23, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 25 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.~~

28.25. A compound of formula (I) according to any one of claims 1 to 21 ~~and 23~~, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 25-24 for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.

29.26. A compound of formula (I) according to any one of claims 1 to 21 ~~and 23~~, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 25-24 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.

30.27. The use of a compound of formula (I) according to any one of claims 1 to 21 ~~and 23~~, 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.

31.28. The use of a compound of formula (I) according to any one of claims 1 to 21 ~~and 23~~, 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.

~~32. — 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 21 and 23, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 25 to the mammal.~~

~~33. — 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 21 and 23, or a
pharmaceutically acceptable salt thereof, or of a pharmaceutical composition
according to claim 25 to the mammal.~~