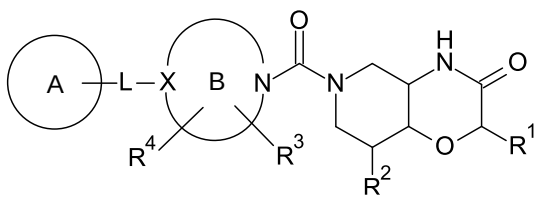
are driven mainly via cannabinoid receptors (CBRs), CB1 and CB2. CB1 receptors are present throughout the GI tract of animals and healthy humans, especially in the enteric nervous system (ENS) and the epithelial lining, as well as smooth muscle cells of blood vessels in the colonic wall (Wright K. *et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

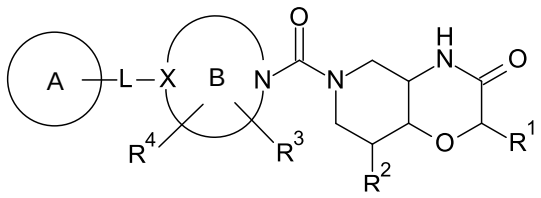
The present disclosure provides a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein A, B, L, X, and R^1 to R^4 are as described herein.

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



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or C-R^5;

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

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

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

A is:

(i) C_{6-14}-aryl substituted with R^6, R^7 and R^8; or

(ii) 5-14 membered heteroaryl substituted with R^9, R^{10} and R^{11}; or

B is a bridged bicyclic heterocycle;

R^1 is hydrogen or C_{1-6}-alkyl;

R^2 is hydrogen or C_{1-6}-alkyl;

R^3 is hydrogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, halogen or hydroxy;

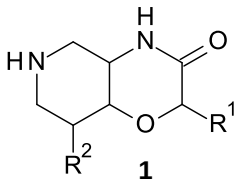
R^4 is hydrogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, halogen or hydroxy;

R^5 is hydrogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, halogen or hydroxy; and

R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from hydrogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, halogen, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, SF_5, C_{1-6}-alkylsulfonyl, cyano, C_{3-10}-cycloalkyl, C_{6-14}-aryl, and 5-14 membered heteroaryl, wherein said C_{3-10}-cycloalkyl, C_{6-14}-aryl, and 5-14 membered heteroaryl are optionally substituted with 1-2 substituents selected from halogen, cyano, SF_5 C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkyl, and halo-C_{1-6}-alkoxy.

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

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



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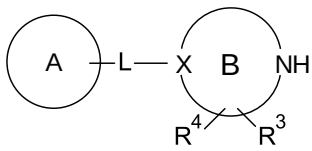
with a secondary amine **2**, wherein A, B, L, X, R^3 and R^4 are as described herein



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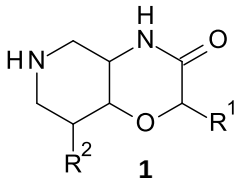
in the presence of a base and a urea forming reagent, to form said compound of formula (I); and optionally

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

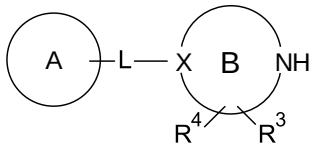
In a further aspect, the present disclosure provides a process of manufacturing the compounds of formula (I) as described herein, or pharmaceutically acceptable salts thereof, comprising:

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



1

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



2

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

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

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

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, mental disorders and/or inflammatory bowel disease in a mammal.

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

In a further aspect, the present disclosure provides 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.

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, 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 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 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

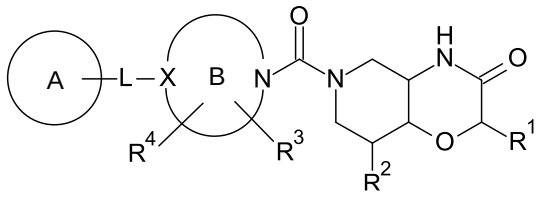
Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein, unless incompatible therewith. All of 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.

The term "alkyl" refers to a mono- or multivalent, e.g., a mono- or bivalent, linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms ("C_1-C_6-alkyl"), e.g., 1, 2, 3, 4, 5, or 6 carbon atoms. In some embodiments, the alkyl group contains 1 to 3 carbon atoms, e.g., 1, 2 or 3 carbon atoms. Some non-limiting examples of alkyl include methyl, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, tert-butyl, and 2,2-dimethylpropyl. A particularly preferred, yet non-limiting example of alkyl is methyl.

The term "alkoxy" refers to an alkyl group, as previously defined, attached to the parent molecular moiety via an oxygen atom. Unless otherwise specified, the alkoxy group contains 1 to 6 carbon atoms ("C_1-C_6-alkoxy"). In some preferred embodiments, the alkoxy group

CLAIMS

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or C-R^5;

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

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

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

A is:

(i) C_{6-14}-aryl substituted with R^6, R^7 and R^8; or

(ii) 5-14 membered heteroaryl substituted with R^9, R^{10} and R^{11}; or

B is a bridged bicyclic heterocycle;

R^1 is hydrogen or C_{1-6}-alkyl;

R^2 is hydrogen or C_{1-6}-alkyl;

R^3 is hydrogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, halogen or hydroxy;

R^4 is hydrogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, halogen or hydroxy;

R^5 is hydrogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, halogen or hydroxy; and

R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently selected from hydrogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, halogen, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, SF_5, C_{1-6}-alkylsulfonyl, cyano, C_{3-10}-cycloalkyl, C_{6-14}-aryl, and 5-14 membered heteroaryl, wherein said C_{3-10}-cycloalkyl, C_{6-14}-aryl, and 5-14 membered heteroaryl are optionally substituted with 1-2 substituents selected from halogen, cyano, SF_5 C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkyl, and halo-C_{1-6}-alkoxy.

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

3. The compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.

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

5. The compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.

6. The compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

7. The compound of formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from hydrogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, and halogen.

8. The compound of formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from halo-C_{1-6}-alkyl and halogen.

9. The compound of formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from CF_3, chloro, and fluoro.

10. The compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from hydrogen and halogen.

11. The compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^7 is halogen.

12. The compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^7 is fluoro or chloro.

13. The compound of formula (I) according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen.

14. The compound of formula (I) according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^9 is selected from hydrogen, C_{3-10}-cycloalkyl, and C_{6-14}-aryl, wherein said C_{6-14}-aryl is substituted with 1-2 substituents selected from halogen and halo-C_{1-6}-alkyl.

15. The compound of formula (I) according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^{10} is selected from hydrogen and halogen.

16. The compound of formula (I) according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^{11} is hydrogen.

17. The compound of formula (I) according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein X is C-R^5.

18. The compound of formula (I) according to any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein L is selected from $–(CH_2)_n-O–$ and $–O-(CH_2)_p–$.

19. The compound of formula (I) according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein n is an integer selected from 0 and 1.

20. The compound of formula (I) according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein p is 1.

21. The compound of formula (I) according to any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein A is C_{6-14}-aryl substituted with R^6, R^7 and R^8.

22. The compound of formula (I) according to any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein A is phenyl substituted with R^6, R^7 and R^8.

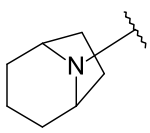
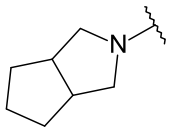
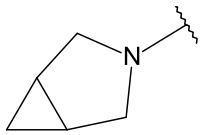
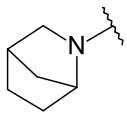
23. The compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein B is a 6-14 membered bridged bicyclic heterocycle comprising 1-3 heteroatoms selected from N, S, and O.

24. The compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein B is a 6-9 membered bridged bicyclic heterocycle comprising 1-2 heteroatoms selected from N and O.

25. The compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein B is a 6-8 membered bridged bicyclic heterocycle comprising 1 nitrogen atom.

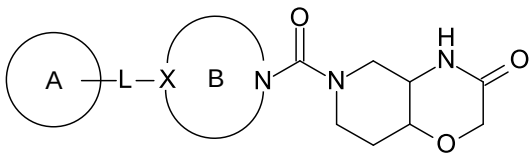
26. The compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein B is selected from 8-

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


(**a**);

(**b**);

(**c**);

(**d**);

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

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


(II)

wherein:

X is N or CH;

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

n is an integer selected from 0 and 1;

A is:

(i) C_{6-14}-aryl substituted with R^6 and R^7; or

(ii) 5-14 membered heteroaryl substituted with R^9 and R^{10}; or

B is a 6-9 membered bridged bicyclic heterocycle comprising 1-2 heteroatoms selected from N and O;

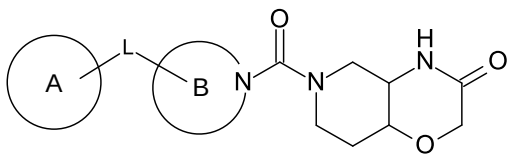
R^6 is selected from hydrogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, and halogen;

R^7 is selected from hydrogen and halogen;

R^9 is selected from hydrogen, C_{3-10}-cycloalkyl, and C_{6-14}-aryl, wherein said C_{6-14}-aryl is substituted with 1-2 substituents selected from halogen and halo-C_{1-6}-alkyl; and

R^{10} is selected from hydrogen and halogen.

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


(III)

wherein:

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

n is an integer selected from 0 and 1;

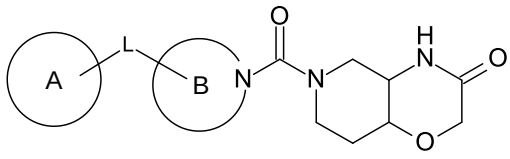
A is C_{6-14}-aryl substituted with R^6 and R^7;

B is a 6-8 membered bridged bicyclic heterocycle comprising 1 nitrogen atom;

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

R^7 is halogen.

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



(III)

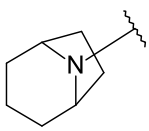
wherein:

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

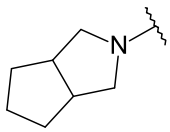
n is an integer selected from 0 and 1;

A is phenyl substituted with R^6 and R^7;

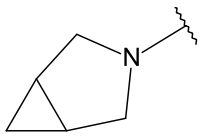
B is selected from 8-azabicyclo[3.2.1]octan-8-yl (**a**); 3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl (**b**); 3-azabicyclo[3.1.0]hexan-3-yl (**c**); and 2-azabicyclo[2.2.1]heptan-2-yl (**d**):



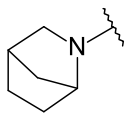
(**a**);



(**b**);



(**c**);



(**d**).

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

R^6 is selected from CF_3, chloro, and fluoro; and

R^7 is fluoro or chloro.

30. The compound of formula (I) according to any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is selected from the compounds disclosed in Table 1.

31. The compound of formula (I) according to any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is selected from the group consisting of:

(4aR,8aS)-6-[(1R,5S,6r)-6-[(2-chloro-4-fluoro-phenoxy)methyl]-3-azabicyclo[3.1.0]hexane-3-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

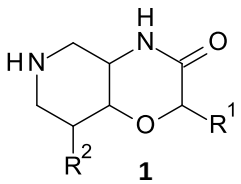
(4aR,8aS)-6-[5-(2-chloro-4-fluoro-phenoxy)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

(4aR,8aS)-6-[rel-(1R,4R,5S)-5-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-2-azabicyclo[2.2.1]heptane-2-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and

(4aR,8aS)-6-[(1S,5R)-3-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-8-azabicyclo[3.2.1]octane-8-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one.

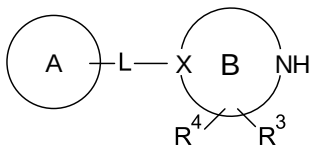
32. A process of manufacturing the compounds of formula (I) according to any one of claims 1 to 31, or pharmaceutically acceptable salts thereof, comprising:

(a) reacting a first amine of formula **1**, wherein R^1 and R^2 are as described in any one of claims 1 to 31,



1

with a second amine **2**, wherein A, B, L, X, R^3 and R^4 are as described in any one of claims 1 to 31



2

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

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

33. A compound of formula (I) according to any one of claims 1 to 31 for use as therapeutically active substance.

34. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 31 and a therapeutically inert carrier.

35. A compound of formula (I) according to any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 34 for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders and/or inflammatory bowel disease in a mammal.

36. A compound of formula (I) according to any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 34 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.

37. The use of a compound of formula (I) according to any one of claims 1 to 31, 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.

38. The use of a compound of formula (I) according to any one of claims 1 to 31, 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.