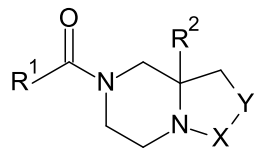
In conclusion, suppressing the action and/or the activation of MAGL is a promising new therapeutic strategy for the treatment or prevention of neuroinflammation, neurodegenerative diseases, pain, cancer and mental disorders. Furthermore, suppressing the action and/or the activation of MAGL is a promising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

Summary ~~of the Invention~~

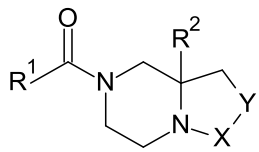
~~In a first aspect, the~~The present ~~invention~~disclosure provides compounds of Formula (I), or pharmaceutically acceptable salts thereof,



(I)

wherein R^1, R^2, X, and Y are as defined herein.

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



(I)

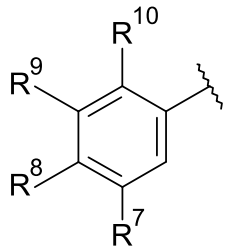
or a pharmaceutically acceptable salt thereof, wherein:

X is $–CH_2CR^3R^4–$ or $–CH=CR^3–$;

Y is –O–, –S–, –SO–, or $–SO_2–$;

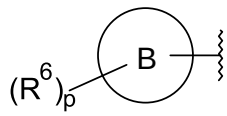
R^1 is

(a) 5- to 14-membered heteroaryl substituted with 1 substituent selected from halogen; or



(b) a group ;

R^2 is hydrogen or C_1-C_6-alkyl;



R^3 is a group ;

R^4 is hydrogen, halogen or hydroxy;

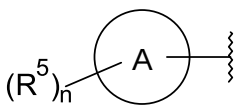
R^5 is hydrogen, halogen, hydroxy, amino, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano or oxo;

R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano; wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with 1-2 substituents selected from halogen, cyano, amino, hydroxy, C_1-C_6-alkyl and C_1-C_6-alkoxy;

R^7 is hydrogen or C_1-C_6-alkoxy;

R^8 is hydrogen or C_1-C_6-alkoxy;

R^9 is hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy or a group



;

R^{10} is hydrogen, halogen, or cyano;

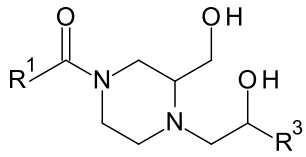
A and B are each independently 5- to 14-membered heteroaryl, C_6-C_{14}-aryl, 3- to 14-membered heterocyclyl or C_3-C_{14}-cycloalkyl; and

n and p are each independently 1, 2, 3, 4 or 5.

~~In a further aspect, the~~The present ~~invention~~disclosure provides a process of manufacturing the compounds of formula (I) as described in any one of the synthetic schemes disclosed herein.

In a further aspect, the present disclosure provides a process of manufacturing the compound of formula (I) as described herein, comprising:

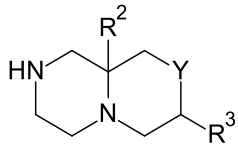
(a) reacting a diol **5**, wherein R^1 and R^3 are as defined herein,



5

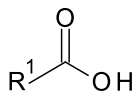
with an etherification reagent, such as (cyanomethylene)tributylphosphorane (CMBP, Tsunoda reagent) to yield said compound of formula (**I**), wherein X is $–CH_2CHR^3–$, Y is –O–, R^1 and R^3 are as defined herein, and R^2 is hydrogen; or

(b) reacting an amine **8a**, wherein Y, R^2 and R^3 are as defined herein,



8a

with a carboxylic acid **1**, wherein R^1 is as defined herein,



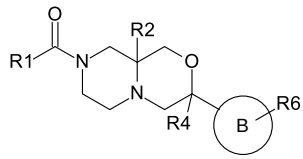
1

in the presence of a base, such as trimethylamine or diisopropylamine, and a coupling reagent, such as HATU, T3P or EDC*HCl, to yield said compound of formula (I), wherein X is $–CH_2CHR^3–$, Y, R^1 and R^3 are as defined herein, and R^2 is hydrogen; or

(c) submitting a compound of formula (I), wherein Y is as defined herein, X is $–CH_2CR^3R^4–$, R^1 to R^3 are as defined herein and R^4 is hydroxy to dehydrating conditions, for example using TES and TFA at elevated temperatures, to yield a compound of formula (I) wherein Y is as defined herein, X is $–CH_2CHR^3–$ and R^1 to R^3 are as defined herein and/or a compound of formula (I) wherein Y is as defined herein, X is $–CH=CR^3–$ and R^1 to R^3 are as defined herein; or

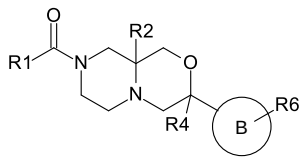
(d) reacting a compound of formula (I), wherein Y is as defined herein, X is $–CH_2CR^3R^4–$, R^1 to R^3 are as defined herein and R^4 is hydroxy, with a nucleophilic fluorinating agent, such as DAST, to yield a compound of formula (I) wherein X is $–CH_2CFR^3–$ and R^1 to R^3 are as defined herein; or

(e) submitting a compound of formula (I),



I

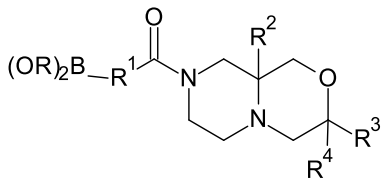
wherein R^1, R^2, R^4, and B are as defined herein, and R^6 is bromo, to a transition metal catalyzed cross-coupling reaction, such as a Suzuki–Miyaura reaction or a Sonogashira reaction, to afford compound of formula (I)



I

wherein R^1, R^2, R^4, and B are as defined herein, and R^6 is selected from aryl, alkenyl, alkynyl, alkyl, cyano, cycloalkyl, and heteroaryl; or

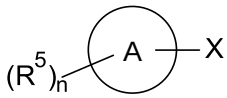
(f) submitting a compound **12**, wherein R^1 is aryl or heteroaryl optionally substituted with 1-4 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, and cyano; and R^2 to R^4 are as defined herein,



12

$B(OR)_2$ = $B(OH)_2$ or boronate pinacol ester

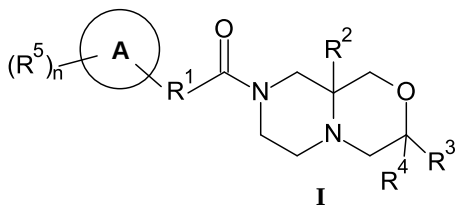
to a Suzuki-Miyaura cross coupling reaction with a compound **13**, wherein A, R^5, and n are as defined herein



13

X = Cl, Br, I, OTf

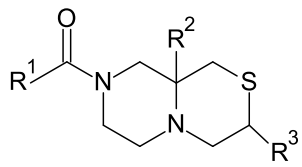
in the presence of a transition metal catalyst, e.g. $PdCl_2$(dppf)-CH_2Cl_2, $Pd_2(dba)_3$ + Xantphos, (A-^{ta}Phos)$_2PdCl_2$, or cataCXium A Pd G2, and an organic or inorganic base such as sodium carbonate, triethylamine, TMEDA or cesium carbonate; to afford said compound of formula (I), wherein R^1 is aryl or heteroaryl optionally substituted with 1-4 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, and cyano; and R^2 to R^5 and n are as defined herein



I

; or

(g) reacting a compound of formula (I), wherein Y is sulfur and R^1, R^2, and R^3 are as defined herein,



I

with an oxidizing agent, such as mCPBA, hydrogen peroxide or sodium periodate, to afford a compound of formula (I), wherein Y is a sulfoxide or a sulfone and R^1, R^2, and R^3 are as defined herein.



I **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 present ~~invention~~disclosure provides a compound of formula (I) as described herein, for use as therapeutically active substance.

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

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

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

In a further aspect, the present disclosure provides the use of a compound of formula (I) 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.

In a further aspect, the present disclosure provides the use of a compound of formula (I) 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 cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with 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

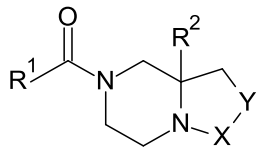
restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method 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. In some preferred embodiments, the alkoxy group contains 1 to 6 carbon atoms (“C_1-C_6-alkoxy”), e.g. 1, 2, 3, 4, 5, or 6 carbon atoms. In other embodiments, the alkoxy group contains 1 to 4 carbon atoms. In still other embodiments, the alkoxy group contains 1 to 3 carbon atoms. Some non-limiting examples of alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy,

CLAIMS

1 A compound of formula (I)



(I)

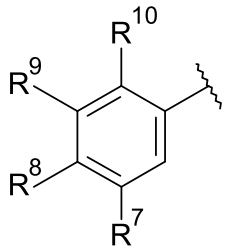
or a pharmaceutically acceptable salt thereof, wherein:

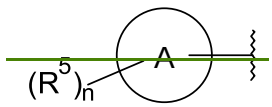
X is $–CH_2CR^3R^4–$ or $–CH=CR^3–$;

Y is –O–, –S–, –SO–, or $–SO_2–$;

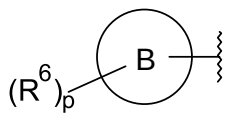
R^1 is

(a) 5- to 14-membered heteroaryl substituted with 1 substituent selected from halogen; or



(b) a group ;~~C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are optionally substituted with 1-5 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, cyano, hydroxy, and a group~~  ;~~;~~

R^2 is hydrogen or C_1-C_6-alkyl;



R^3 is a group ;

R^4 is hydrogen, halogen or hydroxy;

R^5 is hydrogen, halogen, hydroxy, amino, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano or oxo;

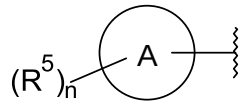
R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-

C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano; wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with 1-2 substituents selected from halogen, cyano, amino, hydroxy, C_1-C_6-alkyl and C_1-C_6-alkoxy;

R^7 is hydrogen or C_1-C_6-alkoxy;

R^8 is hydrogen or C_1-C_6-alkoxy;

R^9 is hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy or a group



;

R^{10} is hydrogen, halogen, or cyano;

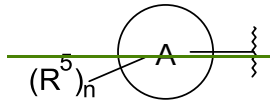
A and B are each independently 5- to 14-membered heteroaryl, C_6-C_{14}-aryl, 3- to 14-membered heterocyclyl or C_3-C_{14}-cycloalkyl; and

n and p are each independently 1, 2, 3, 4 or 5.

2 The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X is $–CH_2CR^3R^4–$.

3 The compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Y is –O– or –S–.

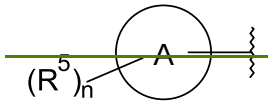
4 The compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Y is –O–.

~~5 The compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are substituted with 1-3 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, halogen, cyano and a group~~ 

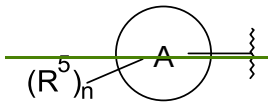
~~.~~

~~6 The compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_6-C_{14}-aryl substituted with~~

~~2-3 substituents independently selected from C_1-C_6-alkoxy, halogen, and a group~~



~~7 The compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl substituted with 2-3 substituents independently selected from chloro, fluoro, methoxy and a group~~



~~8~~5 The compound of formula (I) according to any one of claims 1 to ~~7~~4, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.

~~9~~6 The compound of formula (I) according to any one of claims 1 to ~~8~~5, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen or hydroxy.

~~10~~7 The compound of formula (I) according to any one of claims 1 to ~~9~~6, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, cyano or oxo.

~~11~~8 The compound of formula (I) according to any one of claims 1 to ~~9~~6, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, halogen, cyano, hydroxy or oxo.

~~12~~9 The compound of formula (I) according to any one of claims 1 to ~~9~~6, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, fluoro, cyano, hydroxy or oxo.

~~13~~10 The compound of formula (I) according to any one of claims 1 to ~~12~~9, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano, wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with a substituent selected from halogen, C_1-C_6-alkyl and C_1-C_6-alkoxy.

~~14~~11 The compound of formula (I) according to any one of claims 1 to ~~12~~9, or a pharmaceutically acceptable salt thereof, wherein R^6 is halogen, oxo, halo-C_1-C_6-alkyl or halo-C_1-C_6-alkoxy.

~~15~~12 The compound of formula (I) according to any one of claims 1 to ~~12~~9, or a pharmaceutically acceptable salt thereof, wherein R^6 is chloro, fluoro, oxo, trifluoromethyl or difluoromethoxy.

~~16~~13 The compound of formula (I) according to any one of claims 1 to ~~15~~12, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

~~17~~14 The compound of formula (I) according to any one of claims 1 to ~~16~~13, or a pharmaceutically acceptable salt thereof, wherein p is 1, 2 or 3.

~~18~~15 The compound of formula (I) according to any one of claims 1 to ~~16~~13, or a pharmaceutically acceptable salt thereof, wherein p is 1 or 2.

~~19~~16 The compound of formula (I) according to any one of claims 1 to ~~18~~15, or a pharmaceutically acceptable salt thereof, wherein A is 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl.

~~20~~17 The compound of formula (I) according to any one of claims 1 to ~~18~~15, or a pharmaceutically acceptable salt thereof, wherein A is 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl.

~~21~~18 The compound of formula (I) according to any one of claims 1 to ~~18~~15, or a pharmaceutically acceptable salt thereof, wherein A is imidazolyl, pyrazolyl, pyrrolyl, or 1,2-dihydropyridinyl.

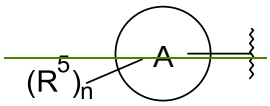
~~22~~19 The compound of formula (I) according to any one of claims 1 to ~~21~~18, or a pharmaceutically acceptable salt thereof, wherein B is C_6-C_{14}-aryl, 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl.

~~23~~20 The compound of formula (I) according to any one of claims 1 to ~~21~~18, or a pharmaceutically acceptable salt thereof, wherein B is phenyl, 1,2-dihydropyridinyl or pyridyl.

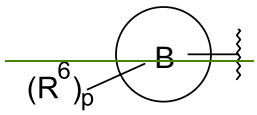
~~24 The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:~~

~~X is $CH_2CR^3R^4$ or $CH=CR^3$;~~

~~Y is O or S;~~

~~R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are substituted with 1-3 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, halogen, cyano and a group~~  ~~;~~

~~R^2 is hydrogen or C_1-C_6-alkyl;~~

~~R^3 is a group~~  ~~;~~

~~R^4 is hydrogen, halogen or hydroxy;~~

~~R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, cyano or oxo;~~

~~R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano, wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with a substituent selected from halogen, C_1-C_6-alkyl and C_1-C_6-alkoxy;~~

~~A and B are each independently 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl;~~

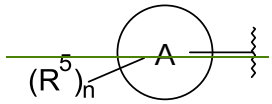
~~n is 1 or 2; and~~

~~p is 1, 2 or 3.~~

~~25 The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:~~

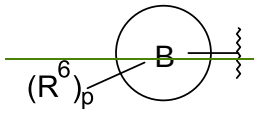
~~X is $CH_2CR^3R^4$;~~

~~Y is O;~~

R^1 is C_6-C_{14}-aryl substituted with 1-2 substituents independently selected from C_1-C_6-alkoxy, halogen, and a group 

;

R^2 is hydrogen;

R^3 is a group 

;

R^4 is hydrogen or hydroxy;

R^5 is hydrogen, halogen, cyano, hydroxy or oxo;

R^6 is halogen, oxo, halo-C_1-C_6-alkyl or halo-C_1-C_6-alkoxy;

A is 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl;

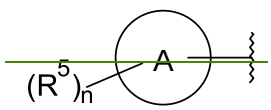
B is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl; and

n and p are each independently 1 or 2.

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

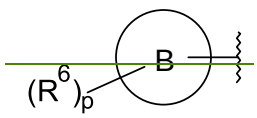
X is $-CH_2CR^3R^4-$;

Y is $-O-$;

R^1 is phenyl substituted with 2-3 substituents independently selected from chloro, fluro, methoxy and a group 

;

R^2 is hydrogen;

R^3 is a group 

;

R^4 is hydrogen or hydroxy;

R^5 is hydrogen, fluoro, cyano, hydroxy or oxo;

R^6 is chloro, fluoro, oxo, trifluoromethyl or difluoromethoxy;

A is imidazolyl, pyrazolyl, pyrrolyl, or 1,2-dihydropyridinyl;

B is phenyl, 1,2-dihydropyridinyl or pyridyl; and

n and p are each independently 1 or 2.

~~27~~21 The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is selected from ~~the compounds of *Table 1*~~:

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

(2-bromo-3-methoxy-phenyl)-[rac-(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

(4-chlorothieno[2,3-b]pyridin-5-yl)-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(3-bromo-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(4-chloro-1H-pyrazolo[3,4-b]pyridin-5-yl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-fluoro-3-methoxy-phenyl)methanone ;

(2-chloro-3-methoxy-phenyl)-[(3R,9aS)-3-[4-fluoro-3-[rac-(E)-prop-1-enyl]phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(4-fluoro-3-phenyl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone ;

[(3S,9aS)-3-(4-fluoro-3-phenyl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(4-fluoro-3-prop-1-ynyl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3,9aS)-3-(3-cyano-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(4-chloro-3-quinolyl)methanone;

[(3S,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3,5-dimethoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3,5-dimethoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3,4-dimethoxy-phenyl)methanone;

2-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-xahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-6-methyl-benzonitrile;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-fluoro-3-(trifluoromethoxy)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-phenyl-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(2-methoxyphenyl)phenyl]methanone;

[(3R,9aS)-3-(3-cyclopropyl-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(difluoromethoxy)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(5-methyl-1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(4-methyl-3-pyridyl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-methyl-4-pyridyl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-pyridazin-4-yl-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(2-pyridyl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-pyridazin-3-yl-phenyl)methanone;

(2-chloro-3-methoxy-phenyl)-[(rel-3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-9a-methyl-1,3,4,6,7,9-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone ;

(2-chloro-3-methoxy-phenyl)-[(rel-3S,9aR)-3-(3-chloro-4-fluoro-phenyl)-9a-methyl-1,3,4,6,7,9-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(4-methylpyridazin-3-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(5-methylpyrimidin-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-imidazol-5-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-methyl-2-pyridyl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1,5-dimethylpyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-methylisoxazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(4-chloro-3-methyl-1H-indazol-5-yl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-morpholino-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-triazol-5-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aR)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[3-(3-bicyclo[4.2.0]octa-1,3,5-trienyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

(2-chloro-3-methoxy-phenyl)-[3-[4-(difluoromethyl)phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3S,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-(2,4-dimethylthiazol-5-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

(2-chloro-3-methoxy-phenyl)-[rel-(3R,9aR)-3-(2,4-dimethylthiazol-5-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

(2-chloro-3-methoxy-phenyl)-[rac-(3R,9aR)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

(2-chloro-3-methoxy-phenyl)-[rac-(3S,9aR)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

(2-chloro-3-methoxy-phenyl)-[rac-(3S,9aS)-3-(5-chloro-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone ;

(2-chloro-3-methoxy-phenyl)-[rac-(3R,9aS)-3-(5-chloro-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-(1H-benzimidazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone ;

(2-chloro-3-methoxy-phenyl)-[rel-(3R,9aR)-3-(1H-benzimidazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-[6-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)pyridin-3-yl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

(2-chloro-3-methoxy-phenyl)-[rel-(3R,9aR)-3-(4,5-dichloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone ;

(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-(4,5-dichloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(9aS)-3-[6-(trifluoromethyl)-3-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[(3R,9aS)-3-[4-(difluoromethoxy)phenyl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[(9aS)-3-(6-bromo-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3S,9aS)-3-hydroxy-3-(1-methylbenzimidazol-2-yl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

5-[(3R,9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-2-fluoro-benzonitrile;

(2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl)((9aS)-3-(4-(difluoromethoxy)phenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

3-[(3S,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one;

3-[(3R,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-oxazol-5-yl-phenyl)methanone;

3-[(3R,9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one;

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

4-[3-[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrazole-3-carbonitrile;

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-pyrazol-4-yl)phenyl]methanone;

(2-chloro-3-methoxyphenyl)((3S,9aS)-3-(5-chloro-4-methylpyridin-2-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone ;

(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(5-chloro-4-methylpyridin-2-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

[(3S,9aS)-3-hydroxy-3-[5-(trifluoromethyl)-2-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3S,9aS)-3-hydroxy-3-[5-(trifluoromethyl)-2-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-oxazol-4-yl-phenyl)methanone;

[3-(1,3-benzothiazol-2-yl)-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[(3S,9aS)-3-fluoro-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[6-(trifluoromethyl)pyridazin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(4-chloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone ;

[(3S,9aS)-3-(4-chloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone ;

[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(9aS)-3-[5-(trifluoromethyl)-2-pyridyl]-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3,4-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone ;

[(3S,9aS)-3-(3,4-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3S,9aS)-3-[6-(trifluoromethyl)pyridazin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[5-chloro-4-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[4-(trifluoromethoxy)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

3-[(3R,9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-3-yl]-6-(trifluoromethyl)-1H-pyridin-2-one;

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[5-fluoro-4-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-fluoro-3-[5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[3-[5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]methanone;

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[4-(difluoromethyl)-5-fluoro-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyridin-2-one;

5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyridin-2-one;

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[5-chloro-4-bromo-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-hydroxyazetidin-1-yl)phenyl]methanone;

4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrrole-2-carbonitrile;

[(3R,9aS)-3-(4-bromo-3-chloro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-6-fluoro-3-methoxy-phenyl)methanone;

4-[3-[(3R,9aS)-3-[2-oxo-6-(trifluoromethyl)-1H-pyridin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyrrole-2-carbonitrile;

4-[3-[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrrole-2-carbonitrile;

4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyridin-2-one;

4-[3-[(3R,9aS)-3-(5-chloro-2-oxo-1H-pyridin-3-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyrrole-2-carbonitrile;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-6-fluoro-3-methoxy-phenyl)methanone;

4-[3-[(3R,9aS)-3-(5-chloro-2-oxo-1H-pyridin-3-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrrole-2-carbonitrile;

5-[3-[(3R,9aS)-3-(3,4-dichlorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-3H-oxazol-2-one;

[(3R,9aS)-3-hydroxy-3-[4-(trifluoromethyl)phenyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(4-chloro-3-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-3H-oxazol-2-one;

5-[3-[(3R,9aS)-3-(3,4-dichlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-3H-oxazol-2-one;

4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-6-methyl-1H-pyridin-2-one;

5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-6-methyl-1H-pyridin-2-one;

[(3R,9aS)-3-(3-bromo-5-chloro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]piperazin-2-one;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-isothiazol-4-yl-phenyl)methanone;

[(3R,9aS)-3-(2,4,5-trifluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(2,4-dichlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-hydroxy-3-(2,3,4-trifluorophenyl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aS)-3-(4-bromo-5-methoxy-2-thienyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

4-[3-[(3R,9aS)-3-[4-oxo-6-(trifluoromethyl)-1H-pyridin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyrrole-2-carbonitrile;

3-[(3R,9aS)-8-[2-chloro-5-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one;

5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-3H-1,3,4-oxadiazol-2-one;

5-[(3R,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-3-chloro-2-fluoro-benzonitrile;

3-[(3R,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-3-yl]-6-(trifluoromethyl)-1H-pyridin-2-one;

[(3R,9aS)-3-(3-chloro-4-oxazol-5-yl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

3-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrazole-5-carbonitrile;

[(3S,9aS)-3-[2-(4-fluorophenyl)thiazol-4-yl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

3-[(3R,9aS)-8-[2-chloro-3-(4-fluoro-1H-pyrazol-3-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one;

[(3R,9aS)-3-hydroxy-3-[3-(trifluoromethyl)phenyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(2,3-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aS)-3-hydroxy-3-(3-phenylisoxazol-5-yl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-hydroxy-3-(2,4,5-trifluorophenyl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(9aS)-3-(4-fluoro-3-oxazol-5-yl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aS)-3-(1,3-benzothiazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

3-[(3R,9aS)-8-(2-chloro-6-fluoro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one;

[(3S,9aS)-3-[5-chloro-6-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(2,3-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(2-chlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

4-[3-[(3S,9aS)-3-[4-oxo-6-(trifluoromethyl)-1H-pyridin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyrrole-2-carbonitrile;

5-[3-[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-imidazole-2-carbonitrile;

[(3R,9aS)-3-hydroxy-3-[2-methyl-6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-5-oxazol-5-yl-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

3-[(3R,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-6-(trifluoromethyl)-1H-pyridin-2-one;

[(9aS)-3-[4-fluoro-3-(1-methylpyrrol-3-yl)phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aS)-3-(3-bromoisoxazol-5-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyridazin-4-one;

[(3S,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-6-fluoro-3-methoxy-phenyl)methanone;

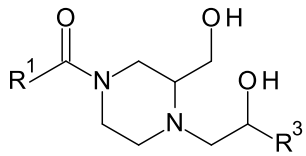
[(3S,9aS)-3-hydroxy-3-[2-(6-methoxy-3-pyridyl)thiazol-4-yl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]thiazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone; and

[(9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]thiazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone.

~~28~~22 A process of manufacturing the compounds of formula (I) according to any one of claims 1 to ~~27~~21, comprising:

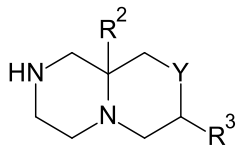
(a) reacting a diol **5**, wherein R^1 and R^3 are as defined herein,



5

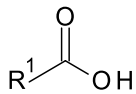
with an etherification reagent, such as (cyanomethylene)tributylphosphorane (CMBP, Tsunoda reagent) to yield said compound of formula (**I**), wherein X is $–CH_2CHR^3–$, Y is –O–, R^1 and R^3 are as defined herein, and R^2 is hydrogen; or

(b) reacting an amine **8a**, wherein Y, R^2 and R^3 are as defined herein,



8a

with a carboxylic acid **1**, wherein R^1 is as defined herein,



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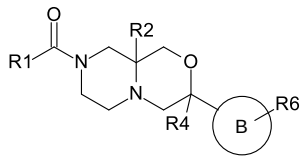
in the presence of a base, such as trimethylamine or diisopropylamine, and a coupling reagent, such as HATU, T3P or EDC*HCl, to yield said compound of formula (I), wherein X is $–CH_2CHR^3–$, Y, R^1 and R^3 are as defined herein, and R^2 is hydrogen; or

(c) submitting a compound of formula (I), wherein Y is as defined herein, X is $–CH_2CR^3R^4–$, R^1 to R^3 are as defined herein and R^4 is hydroxy to dehydrating conditions, for example using TES and TFA at elevated temperatures, to yield a compound of formula (I) wherein Y is as defined herein, X is $–CH_2CHR^3–$ and R^1 to R^3 are as defined herein and/or a compound of formula (I) wherein Y is as defined herein, X is $–CH=CR^3–$ and R^1 to R^3 are as defined herein; or

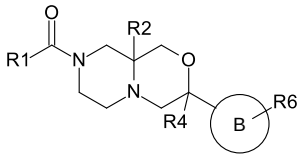
(d) reacting a compound of formula (I), wherein Y is as defined herein, X is $–CH_2CR^3R^4–$, R^1 to R^3 are as defined herein and R^4 is hydroxy, with a nucleophilic fluorinating agent, such as DAST, to yield a compound of formula (I) wherein X is $–CH_2CFR^3–$ and R^1 to R^3 are as defined herein; or

(e) submitting a compound of formula (I),



I

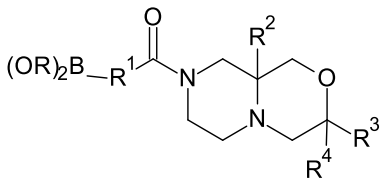
wherein R^1, R^2, R^4, and B are as defined herein, and R^6 is bromo, to a transition metal catalyzed cross-coupling reaction, such as a Suzuki–Miyaura reaction or a Sonogashira reaction, to afford compound of formula (I)



I

wherein R^1, R^2, R^4, and B are as defined herein, and R^6 is selected from aryl, alkenyl, alkynyl, alkyl, cyano, cycloalkyl, and heteroaryl; or

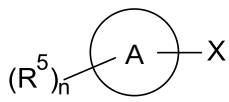
(f) submitting a compound **12**, wherein R^1 is aryl or heteroaryl optionally substituted with 1-4 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, and cyano; and R^2 to R^4 are as defined herein,



12

$B(OR)_2$ = $B(OH)_2$ or boronate pinacol ester

to a Suzuki-Miyaura cross coupling reaction with a compound **13**, wherein A, R^5, and n are as defined herein

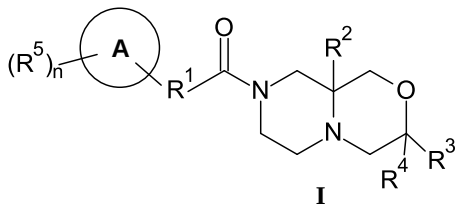


13

X = Cl, Br, I, OTf

in the presence of a transition metal catalyst, e.g. $PdCl_2$(dppf)-CH_2Cl_2, $Pd_2(dba)_3$ + Xantphos, (A-^{ta}Phos)$_2PdCl_2$, or cataCXium A Pd G2, and an organic or inorganic base such as sodium carbonate, triethylamine, TMEDA or

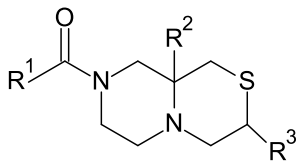
cesium carbonate; to afford said compound of formula (I), wherein R^1 is aryl or heteroaryl optionally substituted with 1-4 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, and cyano; and R^2 to R^5 and n are as defined herein



I

; or

(g) reacting a compound of formula (I), wherein Y is sulfur and R^1, R^2, and R^3 are as defined herein,



I

with an oxidizing agent, such as mCPBA, hydrogen peroxide or sodium periodate, to afford a compound of formula (I), wherein Y is a sulfoxide or a sulfone and R^1, R^2, and R^3 are as defined herein.



I **I**

~~29 A compound of formula (I) according to any one of claims 1 to 27, when manufactured according to the process of claim 28.~~

~~30 The compound of formula (I) according to any one of claims 1 to 27 and 29, wherein said compound of formula (I) has an IC_{50} for monoacylglycerol lipase below 10 µM.~~

~~31~~23 A compound of formula (I) according to any one of claims 1 to ~~27, 29 and 30~~21 for use as therapeutically active substance.

~~32~~24 A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to ~~27, 29 and 30~~21 and a therapeutically inert carrier.

~~33 The use of a compound of formula (I) according to any one of claims 1 to 27, 29 and 30 for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.~~

~~34 The use of a compound of formula (I) according to any one of claims 1 to 27, 29 and 30 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.~~

~~35~~25 A compound of formula (I) according to any one of claims 1 to ~~27, 29 and 30~~21 for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

~~36~~26 A compound of formula (I) according to any one of claims 1 to ~~27, 29 and 30~~21 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.

~~37~~27 The use of a compound of formula (I) according to any one of claims 1 to ~~27, 29 and 30 for~~ 21 in the preparation of a medicament for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

~~38~~28 The use of a compound of formula (I) according to any one of claims 1 to ~~27, 29 and 30 for~~ 21 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.

~~39 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) according to any one of claims 1 to 27, 29 and 30 to the mammal.~~

~~40 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) according to any one of claims 1 to 27, 29 and 30 to the mammal.~~