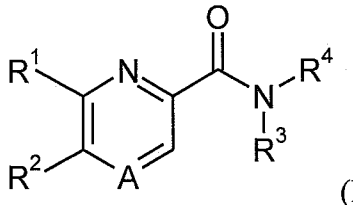
165(4): 951), osteoporosis and inflammation (Sophocleous, A. Calcif Tissue Int 2008, 82(Suppl. 1):Abst OC18), psychiatric diseases and psychosis (Garcia-Gutierrez, M.S. Br J Pharmacol 2012, 165(4): 951), oncology (Preet, A. Cancer Prev Res 2011, 4: 65), encephalitis and malaria (Zimmer, A. WO 2011045068), allergy and inflammation (Ueda, Y. Life Sci 2007, 80(5): 414), encephalitis and malaria (Zimmer, WO 2011045068), asthma (Lunn, C.A. J Pharmacol Exp Ther 2006, 316(2): 780), immunological disorders (Fakhfouri, G. Neuropharmacology 2012, 63(4): 653), rheumatoid arthritis (Chackalamannil, S. US 7776889), arthritis (Lunn, C.A. J Pharmacol Exp Ther 2006, 316(2): 780), and gastrointestinal disorders (Barth, F. FR 2887550),

The compounds of the disclosure bind to and modulate the CB2 receptor and have lower CB1 receptor activity.

In one aspect, there is provided a compound of formula (I)



(I)

wherein

A is -CH- or nitrogen;

R^1 is halophenyl, halophenylalkyl, haloalkoxy, halogen, alkoxyalkoxy, oxopyrrolidinyl or cycloalkylalkoxy;

R^2 is hydrogen, halophenylamino, cycloalkyl or haloazetidinyl;

one of R^3 and R^4 is hydrogen and the other one is $-(CR^5R^6)_m-(CH_2)_n-R^7$;

R^5 and R^6 are independently selected from hydrogen and alkyl;

R^7 is 3-alkoxyalkoxyalkyl-1,2-oxazolyl, 3-oxanyloxyalkyl-1,2-oxazol-5-yl or 3-azidoalkyl-1,2-oxazol-5-yl;

m is 0 or 1;

n is 0 or 1;

In another aspect, there is provided a compound as defined herein for use as therapeutically active substance.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

In another aspect, there is provided the use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy.

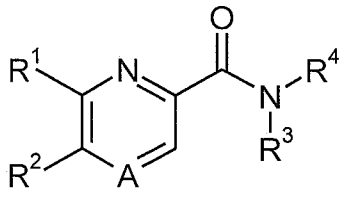
In another aspect, there is provided a compound as defined herein for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy.

In the present description the term "alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, particularly a straight or branched-chain alkyl group with 1 to 6 carbon atoms and more particularly a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched-chain C1-C8 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, particularly methyl, ethyl, propyl, butyl and pentyl. Particular examples of alkyl are methyl, ethyl, isopropyl, butyl, isobutyl, tert.-butyl and pentyl. Methyl is a particular example of alkyl in the compound of formula (I).

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and particularly a cycloalkyl ring with 3 to 6 carbon atoms. Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, cycloheptyl and cyclooctyl. Particular examples of "cycloalkyl" are cyclopropyl, cyclobutyl and cyclopentyl.

Claims

1. A compound of formula (I)



(I)

wherein

A is -CH- or nitrogen;

R^1 is halophenyl, halophenylalkyl, haloalkoxy, halogen, alkoxyalkoxy, oxopyrrolidinyl or cycloalkylalkoxy;

R^2 is hydrogen, halophenylamino, cycloalkyl or haloazetidinyl;

one of R^3 and R^4 is hydrogen and the other one is $-(CR^5R^6)_m-(CH_2)_n-R^7$;

R^5 and R^6 are independently selected from hydrogen and alkyl;

R^7 is 3-alkoxyalkoxyalkyl-1,2-oxazolyl, 3-oxanyloxyalkyl-1,2-oxazol-5-yl or 3-azidoalkyl-1,2-oxazol-5-yl;

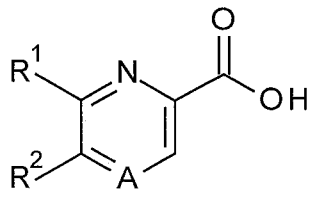
m is 0 or 1;

n is 0 or 1;

or a pharmaceutically acceptable salt or ester thereof..

2. A compound according to claim 1, wherein R^1 is halogen or cycloalkylalkoxy.

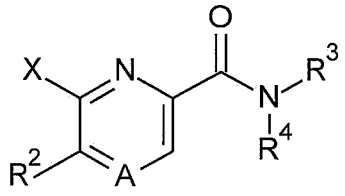
3. A compound according to claim 1 or 2, wherein R^1 is chloro or cyclopropylmethoxy.



(A)

in the presence of NHR^3R^4, an amide coupling agent and a base, wherein A and R^1 to R^4 are as defined in any one of claims 1 to 7;

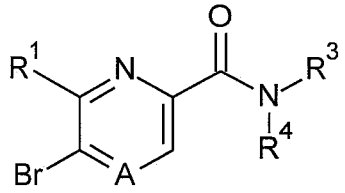
(b) the reaction of a compound of formula (B)



(B)

in the presence of R^1-Y, a palladium catalyst and a base, wherein X is Cl, Br, I or trifluoromethanesulfonate, Y is a trifluoroborate group, a boronic acid group or a boronic acid pinacol ester group, R^1 is halophenyl or halophenylalkyl and A and R^2 to R^4 are as defined in any one of claims 1 to 7; or

(c) the reaction of a compound of formula (C)



(C)

in the presence of R^2-M, a palladium catalyst and a base, wherein R^1 is halophenyl, halophenylalkyl or oxopyrrolidinyl, R^2 is cycloalkyl, A and R^3-R^4 are as defined in any one of claims 1 to 7 and M is a trifluoroborate group, a boronic acid group or a boronic acid pinacol ester group.

11. A compound according to any one of claims 1 to 9 for use as therapeutically active substance.

12. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 9 and a therapeutically inert carrier.

13. The use of a compound according to any one of claims 1 to 9 for the preparation of a medicament for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy.

14. A compound according to any one of claims 1 to 9 for the treatment or prophylaxis of pain, neuropathic pain, asthma, osteoporosis, inflammation, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis or allergy.

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