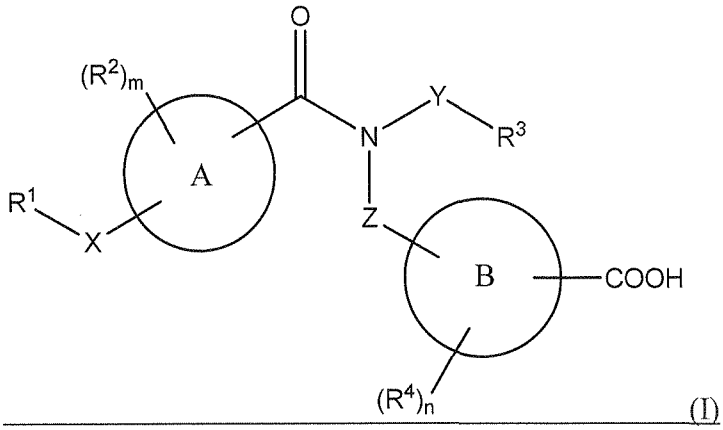
There are currently very few potent LPAR5-selective antagonists. 'LPA5-antagonist 4' has been published by Sanofi-Aventis (Kozian et al, 2012, Bioorg Med Chem Lett., 22(16):5239-43) and is reported to be of low potency against LPAR5 (0.8μM).

It would be desirable to develop compounds that are potent against LPAR5 and/or LPAR1 for use in treating pain disorders and diseases such as atherosclerosis in which these receptors are believed to play a role.

Summary

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



(I)

wherein

R^1 represents a C_5-C_{10} aryl group substituted by at least one substituent selected from halogen, cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxycarbonylamino, C_1-C_6 haloalkoxy, $-NR^5R^6$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkylcarbonylamino, sulphonamido, C_1-C_6 alkylsulphonyl, C_1-C_6 alkylsulphonylamino, $-C(O)NR^7R^8$, C_1-C_6 alkyl which alkyl group may in turn be optionally substituted by at least one halogen, hydroxyl, carboxyl or C_1-C_6 alkoxycarbonyl group, and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring itself being optionally substituted by at least one substituent selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl and C_1-C_6 hydroxyalkyl;

X represents an oxygen atom or a group $-CH_2-$, $-OCH_2-$, $-CH_2O-$, $-CH_2CH_2-$, $-CH_2NR^{17}-$, $-NR^{17}CH_2-$, -CHF- or $-CF_2-$;

m is 0, 1 or 2;

each R^2 independently represents a halogen atom or a hydroxyl, C_1-C_6 alkyl, difluoromethyl, trifluoromethyl, C_1-C_6 alkoxy, difluoromethoxy, trifluoromethoxy or $NR^{15}R^{16}$ group;

Y represents CR^9R^{10} in which R^9 and R^{10} each independently represent a hydrogen atom or a methyl group;

R^3 represents C_1-C_8 alkyl, C_2-C_8 alkenyl, or a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each of the preceding groups being optionally substituted by at least one substituent selected from halogen, cyano, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_5-C_6 aryloxy, C_5-C_6arylC_1-C_6alkyloxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxycarbonylamino, C_1-C_6 alkoxycarbonyloxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NR^{13}R^{14}$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkylcarbonylamino, sulphonamido, C_1-C_6 alkylsulphonyl, C_1-C_6 alkylsulphonylamino, C_1-C_6 alkyl, and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system itself being optionally substituted by least one substituent selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl and C_1-C_6 hydroxyalkyl;

Z represents $CR^{11}R^{12}$ in which R^{11} and R^{12} each independently represent a hydrogen atom or a methyl group but cannot both simultaneously represent a methyl group;

n is 0, 1 or 2;

each R^4 independently represents a halogen atom or a hydroxyl, C_1-C_6 alkyl, difluoromethyl, trifluoromethyl, C_1-C_6 alkoxy, difluoromethoxy, trifluoromethoxy or $NR^{18}R^{19}$ group;

R^5 and R^6 each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^7 and R^8 each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{13} and R^{14} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{15} and R^{16} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{17} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{18} and R^{19} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle; and

rings A and B each independently represent a saturated or unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:

4-((*N*-Ethyl-4-(2-fluorophenoxy)benzamido)methyl)benzoic acid,

4-((*N*-(2,2-Difluoroethyl)-4-(2-fluorophenoxy)benzamido)methyl)benzoic acid,

4-((4-(2-Fluorophenoxy)-*N*-(2,2,2-trifluoroethyl)benzamido)methyl)benzoic acid,
4-((4-(2-Fluorophenoxy)-*N*-isobutylbenzamido)methyl)benzoic acid,
4-((*N*-(Cyclopropylmethyl)-4-(2-fluorophenoxy)benzamido)methyl)benzoic acid,
4-((*N*-(Cyclobutylmethyl)-4-(2-fluorophenoxy)benzamido)methyl)benzoic acid,
4-((4-(2-Fluorophenoxy)-*N*-((3-methoxycyclobutyl)methyl)benzamido)methyl)benzoic acid,
4-((4-(2-Fluorophenoxy)-*N*-isopentylbenzamido)methyl)benzoic acid,
4-((*N*-(2-Cyclopropylethyl)-4-(2-fluorophenoxy)benzamido)methyl)benzoic acid,
4-((*N*-(2-Cyclobutylethyl)-4-(2-fluorophenoxy)benzamido)methyl)benzoic acid,
4-((*N*-Benzyl-4-(2-fluorophenoxy)benzamido)methyl)benzoic acid,
4-((*N*-(2-Fluorobenzyl)-4-(2-fluorophenoxy)benzamido)methyl)benzoic acid,
4-((4-(2-Fluorophenoxy)-*N*-(3-methoxybenzyl)benzamido)methyl)benzoic acid,
4-((4-(2-Fluorophenoxy)-*N*-(4-methoxybenzyl)benzamido)methyl)benzoic acid,
4-((4-(2-Fluorophenoxy)-*N*-phenethylbenzamido)methyl)benzoic acid,
4-((4-(2-Fluorophenoxy)-*N*-(3-(2-fluorophenyl)propyl)benzamido)methyl)benzoic acid,
4-((4-(2-Fluorophenoxy)-*N*-(3-(3-fluorophenyl)propyl)benzamido)methyl)benzoic acid,
4-((4-(2-Fluorophenoxy)-*N*-((*trans*-2-phenylcyclopropyl)methyl)benzamido)-methyl)benzoic acid,
(*S*)-4-((4-(2-Fluorophenoxy)-*N*-(2-hydroxy-3-phenylpropyl)benzamido)methyl)benzoic acid,
(*R*)-4-((4-(2-Fluorophenoxy)-*N*-(2-hydroxy-3-phenylpropyl)benzamido)-methyl)benzoic acid,
4-((4-(2-Fluorophenoxy)-*N*-(4-phenylbutyl)benzamido)methyl)benzoic acid,
4-((*N*-(Cyclopropylmethyl)-4-(*o*-tolyloxy)benzamido)methyl)benzoic acid,
4-((*N*-(Cyclobutylmethyl)-4-(*o*-tolyloxy)benzamido)methyl)benzoic acid,
4-((*N*-Benzyl-4-(*o*-tolyloxy)benzamido)methyl)benzoic acid,
4-((*N*-Phenethyl-4-(*o*-tolyloxy)benzamido)methyl)benzoic acid,
4-((*N*-Phenethyl-4-(2-(trifluoromethyl)phenoxy)benzamido)methyl)benzoic acid,
4-((*N*-Benzyl-4-(2-cyanophenoxy)benzamido)methyl)benzoic acid,
4-((*N*-Ethyl-4-(2-methoxyphenoxy)benzamido)methyl)benzoic acid,
4-((*N*-(2,2-Difluoroethyl)-4-(2-methoxyphenoxy)benzamido)methyl)benzoic acid,

4-((*N*-Isobutyl-4-(2-methoxyphenoxy)benzamido)methyl)benzoic acid,
4-((*N*-(Cyclopropylmethyl)-4-(2-methoxyphenoxy)benzamido)methyl)benzoic acid,
4-((4-(2-Methoxyphenoxy)-*N*-(3-phenylpropyl)benzamido)methyl)benzoic acid,
4-((*N*-(3-(3-Fluorophenyl)propyl)-4-(2-methoxyphenoxy)benzamido)-methyl)benzoic acid,
4-((*N*-(Cyclopropylmethyl)-4-(2-ethoxyphenoxy)benzamido)methyl)benzoic acid,
4-((4-(2-Chlorophenoxy)-*N*-(cyclopropylmethyl)benzamido)methyl)benzoic acid,
4-((4-(2-Chlorophenoxy)-*N*-phenethylbenzamido)methyl)benzoic acid,
4-((*N*-(Cyclopropylmethyl)-4-(2,6-difluorophenoxy)benzamido)methyl)benzoic acid,
4-((*N*-(2-Cyclopropylethyl)-4-(2,6-difluorophenoxy)benzamido)methyl)benzoic acid,
4-((*N*-Benzyl-4-(2,6-difluorophenoxy)benzamido)methyl)benzoic acid,
4-((*N*-(Cyclopropylmethyl)-4-(2-fluoro-6-methylphenoxy)benzamido)methyl)benzoic acid,
4-((*N*-(Cyclobutylmethyl)-4-(2-fluoro-6-methylphenoxy)benzamido)-methyl)benzoic acid,
4-((4-(2-Chloro-6-fluorophenoxy)-*N*-(cyclopropylmethyl)benzamido)methyl)benzoic acid,
4-((4-(2-Chloro-6-fluorophenoxy)-*N*-(2-cyclopropylethyl)benzamido)methyl)benzoic acid,
4-((*N*-Benzyl-4-(2-chloro-6-fluorophenoxy)benzamido)methyl)benzoic acid,
4-((4-(2,6-Dimethylphenoxy)-*N*-isopentylbenzamido)methyl)benzoic acid,
4-((*N*-Benzyl-4-(2,6-dimethylphenoxy)benzamido)methyl)benzoic acid,
4-((4-(2,6-Dimethylphenoxy)-*N*-phenethylbenzamido)methyl)benzoic acid,
4-((4-(3-Methoxyphenoxy)-*N*-phenethylbenzamido)methyl)benzoic acid,
4-((4-(4-Methoxyphenoxy)-*N*-phenethylbenzamido)methyl)benzoic acid,
4-((4-(3-Chlorophenoxy)-*N*-phenethylbenzamido)methyl)benzoic acid,
4-((*N*-(Cyclopropylmethyl)-4-((2-fluorobenzyl)oxy)benzamido)methyl)benzoic acid,
4-((*N*-(Cyclobutylmethyl)-4-((2-fluorobenzyl)oxy)benzamido)methyl)benzoic acid,
4-((*N*-Benzyl-4-((2-fluorobenzyl)oxy)benzamido)methyl)benzoic acid,
4-((*N*-(Cyclopropylmethyl)-2-fluoro-4-(2-fluorophenoxy)-benzamido)methyl)benzoic acid,
4-((*N*-Benzyl-4-(2-fluorophenoxy)cyclohexanecarboxamido)methyl)benzoic acid,

trans-4-((*N*-Benzyl-4-(2-methoxyphenoxy)cyclohexanecarboxamido)methyl)benzoic acid,

cis-4-((*N*-(3-(3-Fluorophenyl)propyl)-4-(2-methoxyphenoxy)cyclohexanecarboxamido)methyl)benzoic acid,

trans-4-((*N*-(3-(3-Fluorophenyl)propyl)-4-(2-methoxyphenoxy)cyclohexanecarboxamido)methyl)benzoic acid

2-Fluoro-4-((4-(2-fluorophenoxy)-*N*-(3-methoxybenzyl)benzamido)-methyl)benzoic acid,

4-((4-(2-Fluorophenoxy)-*N*-propylbenzamido)methyl)benzoic acid,

4-((4-(2-Methoxyphenoxy)-*N*-(2,2,2-trifluoroethyl)benzamido)methyl)benzoic acid,

4-((4-(2-methoxyphenoxy)-*N*-propylbenzamido)methyl)benzoic acid,

4-((*N*-(2,2-difluoropropyl)-4-(2-methoxyphenoxy)-benzamido)methyl)benzoic acid,

4-((4-(2-methoxyphenoxy)-*N*-(3,3,3-trifluoropropyl)-benzamido)methyl)benzoic acid,

4-((*N*-butyl-4-(2-methoxyphenoxy)benzamido)methyl)benzoic acid,

4-((*N*-(cyclopropylmethyl)-2-fluoro-4-(2-methoxyphenoxy)-benzamido)methyl)benzoic acid,

4-((*N*-(cyclopropylmethyl)-4-(2-fluoro-6-methoxyphenoxy)-benzamido)methyl)benzoic acid,

4-((*N*-(cyclopropylmethyl)-4-(4-fluoro-2-methoxyphenoxy)-benzamido)methyl)benzoic acid,

4-((*N*-(cyclopropylmethyl)-5-(2-methoxyphenoxy)-picolinamido)methyl)benzoic acid,

4-((4-(*o*-Tolyloxy)-*N*-(2,2,2-trifluoroethyl)benzamido)methyl)benzoic acid,

4-((4-(2-Fluorophenoxy)-*N*-(3,3,3-trifluoropropyl)benzamido)methyl)benzoic acid,

4-((4-(2-Chlorophenoxy)-*N*-(2,2,2-trifluoroethyl)benzamido)methyl)benzoic acid,

4-((*N*-Ethyl-4-(*o*-tolyloxy)benzamido)methyl)benzoic acid,

4-((*N*-(2,2-Difluoropropyl)-4-(2-fluorophenoxy)benzamido)methyl)benzoic acid,

4-((*N*-Butyl-4-(2-fluorophenoxy)benzamido)methyl)benzoic acid,

4-((4-(2-Chlorophenoxy)-*N*-ethylbenzamido)methyl)benzoic acid,

4-((*N*-(Cyclopropylmethyl)-5-(2-fluorophenoxy)picolinamido)methyl)benzoic acid,

4-((4-(2-Chlorophenoxy)-*N*-(2,2-difluoroethyl)benzamido)methyl)benzoic acid,

4-((*N*-(Cyclopropylmethyl)-4-(5-fluoro-2-methoxyphenoxy)benzamido)methyl)benzoic acid,

4-((4-(4-Fluoro-2-methoxyphenoxy)-*N*-propylbenzamido)methyl)benzoic acid,

4-((4-(5-Fluoro-2-methoxyphenoxy)-*N*-propylbenzamido)methyl)benzoic acid,

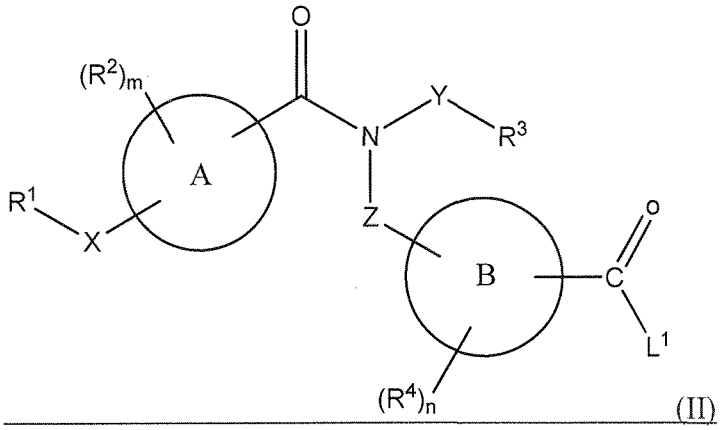
4-((*N*-(Cyclopropylmethyl)-4-(3-fluoro-2-methoxyphenoxy)benzamido)methyl)benzoic acid,

4-((*N*-(Cyclopropylmethyl)-5-(2-fluorophenoxy)pyrimidine-2-carboxamido)methyl)benzoic acid,

4-((*N*-(Cyclopropylmethyl)-5-(2-methoxyphenoxy)pyrimidine-2-carboxamido)methyl)benzoic acid,

4-((5-(2-Methoxyphenoxy)-*N*-propylpyrimidine-2-carboxamido)methyl)benzoic acid, and pharmaceutically acceptable salts thereof.

In another aspect of the present disclosure, there is provided a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein which comprises hydrolysing a compound of formula (II)



(II)

wherein L^1 represents a leaving group and R^1, X, m, R^2, Y, R^3, Z, n, R^4, A and B are as defined in formula (I), in the presence of a suitable base;

and optionally thereafter carrying out one or more of the following procedures:

- converting a compound of formula (I) into another compound of formula (I)
- removing any protecting groups
- forming a pharmaceutically acceptable salt.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt

thereof as defined herein, in association with a pharmaceutically acceptable adjuvant, diluent or carrier, and optionally one or more other therapeutic agents.

In a further aspect of the present disclosure, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein for use in treating a condition whose development or symptoms are linked to LPAR5 activity.

In another aspect of the present disclosure, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein for use in treating a condition whose development or symptoms are linked to LPAR1 activity.

In yet another aspect of the present disclosure, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein for use in treating pain disorders, atherosclerosis or fibrosis.

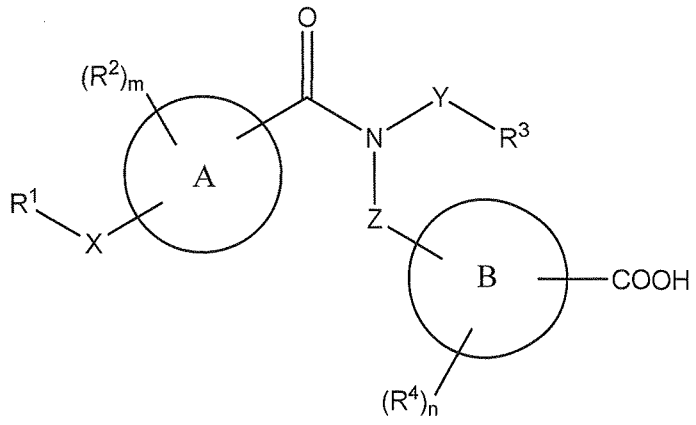
In a further aspect of the present disclosure, there is provided a use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein, in the manufacture of a medicament for treating a condition whose development or symptoms are linked to LPAR5 activity.

In another aspect of the present disclosure, there is provided a use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein, in the manufacture of a medicament for treating a condition whose development or symptoms are linked to LPAR1 activity.

In yet another aspect of the present disclosure, there is provided a use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein, in the manufacture of a medicament for treating pain disorders, atherosclerosis or fibrosis.

Detailed Description

In accordance with the present invention, there is therefore provided a compound of formula (I)



(I)

wherein

R^1 represents a C_5-C_{10} aryl group substituted by at least one substituent independently selected from halogen, cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxycarbonylamino, C_1-C_6 haloalkoxy, $-NR^5R^6$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkylcarbonylamino, sulphonamido ($-SO_2NH_2$), C_1-C_6 alkylsulphonyl, C_1-C_6 alkylsulphonylamino, $-C(O)NR^7R^8$, C_1-C_6 alkyl which alkyl group may in turn be optionally substituted by at least one halogen, hydroxyl, carboxyl or C_1-C_6 alkoxycarbonyl

- converting a compound of formula (I) into another compound of formula (I)
- removing any protecting groups
- forming a pharmaceutically acceptable salt.

15. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 13, in association with a pharmaceutically acceptable adjuvant, diluent or carrier, and optionally one or more other therapeutic agents.

16. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 13 for use in treating a condition whose development or symptoms are linked to LPAR5 activity.

17. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 13 for use in treating a condition whose development or symptoms are linked to LPAR1 activity.

18. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 13 for use in treating pain disorders, atherosclerosis or fibrosis.

19. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 13, in the manufacture of a medicament for treating a condition whose development or symptoms are linked to LPAR5 activity.

20. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 13, in the manufacture of a medicament for treating a condition whose development or symptoms are linked to LPAR1 activity.

21. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 13, in the manufacture of a medicament for treating pain disorders, atherosclerosis or fibrosis.