THERAPEUTIC AGENTS

Field of invention

The present invention relates to certain compounds of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.

Background of the invention

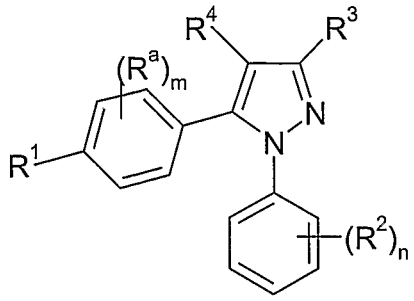
It is known that certain CB_1 modulators (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 EP 658,546 and EP 656,354). However, there is a need for CB_1 modulators with improved physicochemical properties and/or DMPK properties and/or pharmacodynamic properties.

Pyrazoles having anti-inflammatory activity are disclosed in WO 95/15316, WO96/38418, WO97/11704, WO99/64415, EP 418 845 and WO2004050632. WO2004050632 discloses 1,1-dimethylethyl [2-[4-[3-[(ethylmethylamino)carbonyl]-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy]ethyl]carbamate, 5-[4-(2-aminoethoxy)phenyl]-*N*-ethyl-1-(4-methoxyphenyl)-*N*-methyl-1H-pyrazole-3-carboxamide, 1-[[5-[4-(2-aminoethoxy)phenyl]-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]carbonyl]piperidine and 1,1-dimethylethyl [2-[4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1*H*-pyrazol-5-yl]phenoxy]ethyl]-carbamate. All compounds exemplified in WO2004050632 and salts thereof are excluded from the scope of the compound claims of the present invention.

1,5-Diarylpyrazole-3-carboxamide derivatives are disclosed as having CB_1 modulatory activity in US 5,624,941, WO01/29007, WO2004/052864, WO03/020217, US 2004/0119972, Journal of Medicinal Chemistry, 46(4), 642-645 2003, Bioorganic & Medicinal Chemistry Letters, 14(10), 2393-2396 2004, Biochemical Pharmacology, 60(9), 1315-1323 2000, Journal of Medicinal Chemistry, 42(4), 769-776 1999 and U.S. Pat. Appl. Publ. US 2003199536.

Description of the invention

The invention relates to a compound of formula (I)



I

and pharmaceutically acceptable salts thereof, in which

R^1 represents a) a C_{1-3}alkoxy group substituted by one or more of the following i) fluoro ii) a group NR^cR^d in which R^c and R^d independently represent H, a C_{1-6}alkyl group or C_{1-6}alkoxycarbonyl group provided that one of R^c and R^d is other than H or iii) a 1,3-dioxolan-2-yl group b) R^1 represents a C_{4-6}alkoxy group optionally substituted by one or more of the following i) fluoro ii) a group NR^cR^d in which R^c and R^d independently represent H, a C_{1-6}alkyl group or C_{1-6}alkoxycarbonyl group provided that one of R^c and R^d is other than H or iii) a 1,3-dioxolan-2-yl group c) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, d) a group $R^5S(O)_2O$ or $R^5S(O)_2NH$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, or R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z e) a group of formula $(R^6)_3$ Si in which R^6 represents a C_{1-6}alkyl group which may be the same or different or f) a group of formula $R^bO(CO)O$ in which R^b represents a C_{1-6}alkyl group optionally substituted by one or more fluoro;

R^a represents halo, a C_{1-3}alkyl group or a C_{1-3}alkoxy group;

m is 0, 1, 2 or 3;

R^2 represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, nitro, cyano or halo

n is 0, 1, 2 or 3;

R^3 represents

a) a group X-Y-NR^7R^8

in which X is CO or SO_2,

Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group;

and R^7 and R^8 independently represent :

a C_{1-6}alkyl group optionally substituted by 1, 2, or 3 groups represented by W;

a C_{3-15}cycloalkyl group optionally substituted by 1, 2, or 3 groups represented by W;

a (C_{3-15}cycloalkyl)C_{1-3}alkylene group optionally substituted by 1, 2, or 3 groups represented by W;

a group $-(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group, a C_{1-5}alkoxy group or halo wherein the alkyl and alkoxy group are optionally independently substituted by one of more fluoro;

or R^7 represents H and R^8 is as defined above;

or R^7 and R^8 together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy, fluoro or benzyl;

or b) oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thienyl, furyl or oxazolinyl,

each optionally substituted by 1, 2 or 3 groups Z;

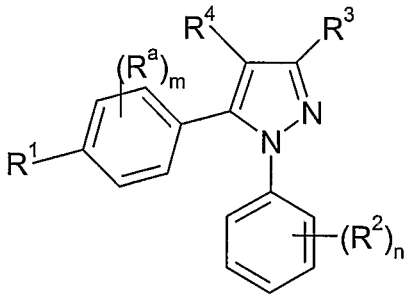
R^4 represents H, halo, hydroxy, cyano, a C_{1-6}alkyl group, a C_{1-6}alkoxy group or a C_{1-6}alkoxyC_{1-6}alkylene group which contains a maximum of 6 carbon atoms, each of which groups is optionally substituted by one or more fluoro or cyano;

Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C_{1-3}alkylamino, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl and acetyl; and

W represents hydroxy, fluoro, a C_{1-3}alkyl group, a C_{1-3}alkoxy group, amino, mono or di C_{1-3}alkylamino, a C_{1-6}alkoxycarbonyl group or a heterocyclic amine selected from morpholinyl, pyrrolidinyl, piperdinyl or piperazinyl in which the heterocyclic amine is optionally substituted by a C_{1-3}alkyl group or hydroxyl;

but excluding 1,1-dimethylethyl [2-[4-[3-[(ethylmethylamino)carbonyl]-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy]ethyl]carbamate and 1,1-dimethylethyl [2-[4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1*H*-pyrazol-5-yl]phenoxy]ethyl]carbamate.

In one embodiment the invention relates to a compound of formula (I)



I

and pharmaceutically acceptable salts thereof, in which

R^1 represents a) a C_{1-3}alkoxy group substituted by one or more fluoro or C_{4-6}alkoxy group optionally substituted by one or more fluoro b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^5S(O)_2O$ or $R^5S(O)_2NH$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, or R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z d) a group of formula $(R^6)_3$ Si in which R^6 represents a C_{1-6}alkyl group which may be the same or different or e) a group of formula $R^bO(CO)O$ in which R^b represents a C_{1-6}alkyl group optionally substituted by one or more fluoro;

R^a represents halo, a C_{1-3}alkyl group or a C_{1-3}alkoxy group

m is 0, 1, 2 or 3;

R^2 represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, nitro, cyano or halo

n is 0, 1, 2 or 3;

R^3 represents

a) a group X-Y-NR^7R^8

in which X is CO or SO_2,

Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group;

and R^7 and R^8 independently represent :

a C_{1-6}alkyl group optionally substituted by 1, 2, or 3 groups represented by W;

a C_{3-15}cycloalkyl group optionally substituted by 1, 2, or 3 groups represented by W;

an optionally substituted (C_{3-15}cycloalkyl)C_{1-3}alkylene group optionally substituted by 1, 2, or 3 groups represented by W;

a group $-(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group, a C_{1-5}alkoxy group or halo;

or R^7 represents H and R^8 is as defined above;

or R^7 and R^8 together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy, fluoro or benzyl;

or b) oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thienyl, furyl or oxazolinyl,

each optionally substituted by 1, 2 or 3 groups Z;

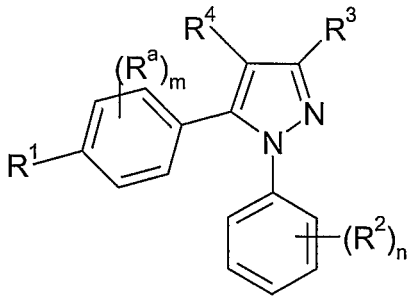
R^4 represents H, halo, hydroxy, cyano, a C_{1-6}alkyl group, a C_{1-6}alkoxy group or a C_{1-6}alkoxyC_{1-6}alkylene group which contains a maximum of 6 carbon atoms, each of which groups is optionally substituted by one or more fluoro or cyano;

Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro,

amino, mono or di C_{1-3}alkylamino, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl and acetyl; and

W represents hydroxy, fluoro, a C_{1-3}alkyl group, a C_{1-3}alkoxy group, amino, mono or di C_{1-3}alkylamino, a C_{1-6}alkoxycarbonyl group or a heterocyclic amine selected from morpholinyl, pyrrolidinyl, piperdinyl or piperazinyl in which the heterocyclic amine is optionally substituted by a C_{1-3}alkyl group or hydroxyl.

In another embodiment the invention relates to a compound of formula (I)



I

and pharmaceutically acceptable salts thereof, in which

R^1 represents a) a C_{1-3}alkoxy group substituted by one or more fluoro or C_{4-6}alkoxy group optionally substituted by one or more fluoro b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^5S(O)_2O$ or $R^5S(O)_2NH$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, or R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z or d) a group of formula $(R^6)_3$ Si in which R^6 represents a C_{1-6}alkyl group which may be the same or different;

R^a represents halo, a C_{1-3}alkyl group or a C_{1-3}alkoxy group

m is 0, 1, 2 or 3;

R^2 represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, nitro, cyano or halo

n is 0, 1, 2 or 3;

R^3 represents

a) a group X-Y-NR^7R^8

in which X is CO or SO_2,

Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group;

and R^7 and R^8 independently represent :

a C_{1-6}alkyl group optionally substituted by 1, 2, or 3 groups represented by W;
a C_{3-15}cycloalkyl group optionally substituted by 1, 2, or 3 groups represented by W;
an optionally substituted (C_{3-15}cycloalkyl)C_{1-3}alkylene group optionally substituted by 1, 2, or 3 groups represented by W;
a group $-(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;
a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;
a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group, a C_{1-5}alkoxy group or halo;
or R^7 represents H and R^8 is as defined above;
or R^7 and R^8 together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy, fluoro or benzyl;
or b) oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thienyl, furyl or oxazolinyl,
each optionally substituted by 1, 2 or 3 groups Z;
R^4 represents H, a C_{1-6}alkyl group, a C_{1-6}alkoxy group or a C_{1-6}alkoxyC_{1-6}alkylene group which contains a maximum of 6 carbon atoms, each of which groups is optionally substituted by one or more fluoro or cyano;
Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C_{1-3}alkylamino, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl and acetyl; and
W represents hydroxy, fluoro, a C_{1-3}alkyl group, a C_{1-3}alkoxy group, amino, mono or di C_{1-3}alkylamino, or a heterocyclic amine selected from morpholinyl, pyrrolidinyl, piperdinyl or

piperazinyl in which the heterocyclic amine is optionally substituted by a C_{1-3}alkyl group or hydroxyl.

In particular groups of compounds of formula I described in the three embodiments above, R^3 represents a group as described in paragraph a) above. In further particular groups of compounds of these three embodiments above in which R^3 represents a group as described in paragraph a) above, compounds in which R^3 represents *N*, *N*-diC_{1-6}alkylcarbamoyl or R^3 represents a group X-Y-NR^7R^8 in which X is CO, Y is absent and R^7 and R^8 together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy, fluoro or benzyl; are excluded. In still further particular groups of compounds of formula I described in the first three embodiments above, R^3 represents piperidin-1-ylcarbamoyl.

It will be understood that where a substituent Z is present in more than one group that these substituents are independently selected and may be the same or different. The same is true for W. Similarly when m is 2 or 3 then the groups R^a are independently selected so that they may be the same or different and similarly when n is 2 or 3 then the groups R^2 are independently selected so that they may be the same or different.

The term C_{3-15}cycloalkyl includes monocyclic, bicyclic, tricyclic and spiro systems for example, cyclopentyl, cyclohexyl and adamantyl.

The term heteroaryl means an aromatic 5-, 6-, or 7-membered monocyclic ring or a 9- or 10-membered bicyclic ring, with up to five ring heteroatoms selected from oxygen, nitrogen and sulfur. Suitable aromatic heteroaryl groups include, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl. Preferably furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, oxazolyl thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl and more preferably pyrrolyl, thienyl, imidazolyl, oxazolyl or pyridyl.

Suitable saturated or partially unsaturated 5 to 8 membered heterocyclic groups containing one or more heteroatoms selected from nitrogen, oxygen or sulphur include, for example tetrahydrofuranyl, tetrahydropyranyl, 2,3-dihydro-1,3-thiazolyl, 1,3-thiazolidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, piperidinyl or piperazinyl, more preferably tetrahydrofuran-3-yl, tetrahydropyran-4-yl, pyrrolidin-3-yl, morpholino, piperidino, piperidin-4-yl or piperazin-1-yl.

Suitable groups in which R^1 represents a group $R^5S(O)_2O$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro include methanesulfonyloxy, ethanesulfonyloxy, n-propylsulfonyloxy, n-butylsulfonyloxy, 3-methylbutane-1-sulfonyloxy, 3,3-dimethylbutane-1-sulfonyloxy, fluoromethylsulfonyloxy, difluoromethylsulfonyloxy, trifluoromethylsulfonyloxy, mono, di or tri (fluoroethyl)sulfonloxy, 3,3,3-trifluoropropyl-1-sulfonyloxy, or 4,4,4-trifluorobutyl-1-sulfonyloxy,

Suitable groups in which R^1 represents a C_{1-3}alkoxy group substituted by one or more fluoro or C_{4-6}alkoxy group optionally substituted by one or more fluoro include butoxy, pentyloxy, hexyloxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, 4,4,4 –trifluorobutoxy, 5,5,5,-trifluoropentyloxy and 6,6,6-trifluorohexyloxy.

Suitable groups in which R^1 represents a group $R^5S(O)_2O$ in which R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z include phenylsulfonyloxy, thienylsulfonyloxy or pyridylsulfonyloxy optionally substituted by 1, 2 or 3 groups represented by Z.

In a particular group of compounds of formula I, R^1 represents a) a C_{1-3}alkoxy group substituted by one or more of the following i) fluoro ii) a group NR^cR^d in which R^c and R^d independently represent H, a C_{1-6}alkyl group or C_{1-6}alkoxycarbonyl group provided that one of R^c and R^d is other than H or iii) a 1,3-dioxolan-2-yl group b) R^1 represents a C_{4-6}alkoxy group optionally substituted by one or more of the following i) fluoro ii) a group NR^cR^d in which R^c and R^d independently represent H, a C_{1-6}alkyl group or C_{1-6}alkoxycarbonyl group provided that one of R^c and R^d is other than H or iii) a 1,3-dioxolan-2-yl group c) a group $R^5S(O)_2O$ in which R^5 represents a C_{1-6}alkyl group

optionally substituted by one or more fluoro, or R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z d) a group of formula $R^bO(CO)O$ in which R^b represents a C_{1-6}alkyl group optionally substituted by one or more fluoro;

R^a represents halo;

m is 0, 1, 2 or 3;

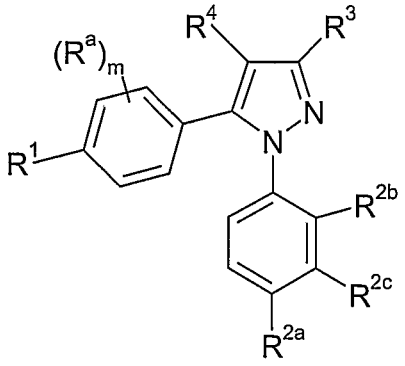
R^2 represents halo;

n is 0, 1, 2 or 3;

R^3 represents a group $CONR^7R^8$ in which R^7 represents H and R^8 represents a C_{3-15}cycloalkyl group optionally substituted by a group represented by W or R^8 represents a group $-(CH_2)_t$ Het in which t is 0 and Het represents pyridyl optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group optionally independently substituted by one of more fluoro; or R^3 represents a group $CONHNR^7R^8$ in which NR^7R^8 represents piperidino or morpholino; and

R^4 represents H, halo or a C_{1-6}alkyl group which is optionally substituted by one or more fluoro; Z represents halo; and W represents a C_{1-6}alkoxycarbonyl group.

A particular group of compounds of formula I is represented by formula IA



IA

in which R^1 is

a) a C_{4-6}alkoxy group optionally substituted by one or more fluoro, b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^5S(O)_2O$ or $R^5S(O)_2NH$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, or R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z wherein Z is as previously defined d) a group of formula $(R^6)_3$ Si in which R^6 represents

a C_{1-6}alkyl group which may be the same or different or e) a group of formula $R^bO(CO)O$ in which R^b represents a C_{1-6}alkyl group optionally substituted by one or more fluoro;

R^a represents halo and m is 0, 1 or 2;

R^{2a} represents chloro;

R^{2b} represents chloro;

R^{2c} represents H or fluoro;

R^3 represents a group $CONHNR^7R^8$ in which NR^7R^8 represents piperidino or morpholino or R^3 represents a group $CONHR^8$ in which R^8 represents a C_{5-7}cycloalkyl group optionally substituted by a C_{1-6}alkoxycarbonyl group or R^8 represents an optionally substituted pyridyl; and

R^4 represents H, a C_{1-3}alkyl group or halo.

A particular group of compounds of formula I is represented by formula IA in which R^1 is a) a C_{4-6}alkoxy group optionally substituted by one or more fluoro, b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^5S(O)_2O$ or $R^5S(O)_2NH$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, or R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z d) a group of formula $(R^6)_3$ Si in which R^6 represents a C_{1-6}alkyl group which may be the same or different or e) a group of formula $R^bO(CO)O$ in which R^b represents a C_{1-6}alkyl group optionally substituted by one or more fluoro;

R^a represents halo and m is 0, 1 or 2;

R^{2a} represents chloro;

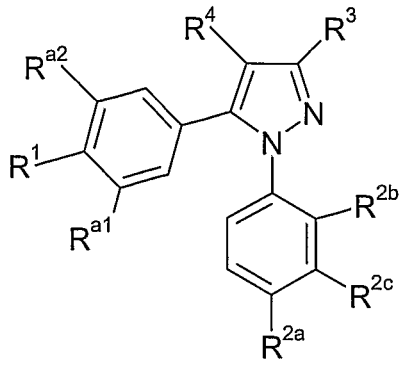
R^{2b} represents chloro;

R^{2c} represents H;

R^3 represents a group $CONHNR^7R^8$ in which NR^7R^8 represents piperidino or morpholino or R^3 represents a group $CONHR^8$ in which R^8 represents a C_{5-7}cycloalkyl group optionally substituted by a C_{1-6}alkoxycarbonyl group; and

R^4 represents a C_{1-3}alkyl group or halo.

A further particular group of compounds of formula I is represented by formula IB



IB

in which R^1 is
a) a C_{4-6}alkoxy group optionally substituted by one or more fluoro, b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^5S(O)_2O$ or $R^5S(O)_2NH$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, or R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z or d) a group of formula $(R^6)_3$ Si in which R^6 represents a C_{1-6}alkyl group which may be the same or different;

R^{a1} represents halo or H;

R^{a2} represents halo or H;

R^{2a} represents chloro;

R^{2b} represents chloro;

R^{2c} represents halo or H;

R^3 represents a group $CONHNR^7R^8$ in which NR^7R^8 represents piperidino; and

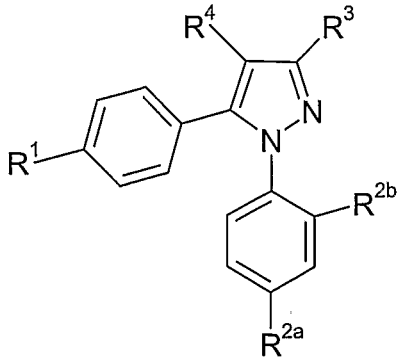
R^4 represents a C_{1-3}alkyl group.

In one particular group of compounds of formula I, formula IA or formula IB, R^1 represents a C_{4-6}alkoxy group optionally substituted by one or more fluoro.

In a further particular group of compounds of formula I, formula IA or formula IB, R^1 represents a group $R^5S(O)_2O$ or $R^5S(O)_2NH$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, or R^5 represents a heteroaryl group optionally substituted by 1, 2 or 3 groups represented by Z. In a yet further group R^1 represents a group $R^5S(O)_2O$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro.

In a still further particular group of compounds of formula I, formula IA or formula IB, R^1 represents a group of formula $(R^6)_3$ Si in which R^6 represents a C_{1-6}alkyl group which may be the same or different.

A particular group of compounds of formula I is represented by formula IC



IC

in which R^1 is

a) a C_{4-6}alkoxy group optionally substituted by one or more fluoro, b) a group $R^5S(O)_2O$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro;

R^{2a} represents chloro;

R^{2b} represents chloro;

R^3 represents a group $CONHNR^7R^8$ in which NR^7R^8 represents piperidino or morpholino; and

R^4 represents a C_{1-3}alkyl group or halo.

In a particular group of compounds of formula IC, R^1 is a group $R^5S(O)_2O$ in which R^5 represents a C_{1-6}alkyl group substituted by one or more fluoro.More particularly R^1 is a group $R^5S(O)_2O$ in which R^5 represents a C_{3-6}alkyl group substituted by one or more fluoro.

Further values of R^1, R^2, R^3, R^4 and R^a in compounds of formula I, formula IA, formula IB, or formula IC now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

R^1 represents 4,4,4 -trifluorobutoxy, n-butylsulfonyloxy, n-propylsulfonyloxy, 4,4,4-trifluorobutyl-1-sulfonyloxy, 3,3,3-trifluoropropyl-1-sulfonyloxy, propoxycarbonyloxy, 2-(1,3-dioxolan-2-yl)ethoxy, *N*-ethyl -2-aminoethoxy, *N*- *tert*-butoxycarbonyl-*N*-ethyl -2-

aminoethoxy, 3-methylbutane-1-sulfonyloxy, 3,3-dimethylbutane-1-sulfonyloxy, 5-chloro-2-thienylsulfonyloxy, 2-thienylsulfonyloxy or 3-pyridylsulfonyloxy.

R^1 represents a C_{4-6}alkoxy group substituted by one or more fluoro. R^1 represents 4,4,4 -trifluorobutoxy, n-butylsulfonyloxy, n-propylsulfonyloxy, 4,4,4-trifluorobutyl-1-sulfonyloxy, 3,3,3-trifluoropropyl-1-sulfonyloxy, propoxycarbonyloxy, 2-(1,3-dioxolan-2-yl)ethoxy, *N*-ethyl -2-aminoethoxy, or *N*- *tert*-butoxycarbonyl-*N*-ethyl -2-aminoethoxy.

R^1 represents 4,4,4 -trifluorobutoxy, n-butylsulfonyloxy, n-propylsulfonyloxy, 4,4,4-trifluorobutyl-1-sulfonyloxy, 3,3,3-trifluoropropyl-1-sulfonyloxy or propoxycarbonyloxy.

R^1 represents 4,4,4 -trifluorobutoxy, n-butylsulfonyloxy or n-propylsulfonyloxy.

R^2 represents chloro or fluoro and n is 2 or 3.

R^3 represents *N*-(piperidin-1-yl)carbamoyl, 5-(trifluoromethyl)pyridin-2-yl]amino}carbonyl, morpholin-4-ylcarbamoyl or *N*-(1-methoxycarbonyl-1-cyclopentyl)carbamoyl.

R^4 represents C_{1-4}alkyl or halo. R^4 represents methyl or bromo.

m is 0 or when m is 1 or 2 R^a represents fluoro.

In a further particular group of compounds of formula I, formula IA, formula IB, or formula IC or any embodiments thereof, R^3 represents N-(piperidin-1-yl)carbamoyl.

"Pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula I is, for example, an acid-addition salt of a compound of Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a sodium, calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates. Isomers may be separated using conventional techniques, e.g.

chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention. All tautomers, where possible, are included within the scope of the invention. The present invention also encompasses compounds containing one or more isotopes for example ^{14}C, ^{11}C or ^{19}F and their use as isotopically labelled compounds for pharmacological and metabolic studies.

The present invention also encompasses prodrugs of a compound of formula I that is compounds which are converted into a compound of formula I in vivo.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl , t-butyl, pentyl, isopentyl, neopentyl, *tert*-pentyl, hexyl and isohexyl. Preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

Specific compounds of the invention are one or more of the following:

butane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

1-(2,4-dichlorophenyl)-4-methyl-5-[4-(4,4,4-trifluorobutoxy)phenyl]-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide;

propane-1-sulfonic acid 4-[2-(2,4-dichloro-phenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)2*H*-pyrazol-3-yl]-phenyl ester;

propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(morpholin-4-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

3,3,3-trifluoropropane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

4,4,4-trifluorobutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

propane-1-sulfonic acid-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]-2,6-difluorophenyl ester;

propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

propane-1-sulfonic acid 4-[4-bromo-2-(2,4-dichlorophenyl)-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

methyl 1-{[(1-(2,4-dichlorophenyl)-4-methyl-5-{4[(propylsulfonyl)oxy]phenyl}-1*H*-pyrazol-3-yl)carbonyl]amino}cyclopentanecarboxylate;

carbonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidine-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]-phenyl ester propyl ester;

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl thiophene-2-sulfonate;

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl pyridine-3-sulfonate;

tert-butyl [2-(4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenoxy)ethyl]ethylcarbamate;

1-(2,4-dichlorophenyl)-5-{4-[2-(ethylamino)ethoxy]phenyl}-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide;

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl 3-methylbutane-1-sulfonate;

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl 3,3-dimethylbutane-1-sulfonate;

4-[1-(2,4-dichlorophenyl)-4-methyl-3-({[5-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)-1*H*-pyrazol-5-yl]phenyl 3,3,3-trifluoropropane-1-sulfonate;

1-(2,4-dichlorophenyl)-5-{4-[2-(1,3-dioxolan-2-yl)ethoxy]phenyl}-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide;

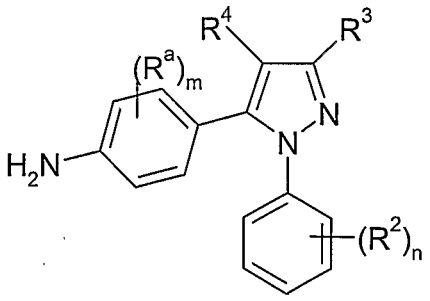
propane-1-sulfonic acid 4-[2-(2,4-dichloro-3-fluorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester; and

5-chloro-thiophene-2-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester;

as well as pharmaceutically acceptable salts thereof.

Methods of preparation

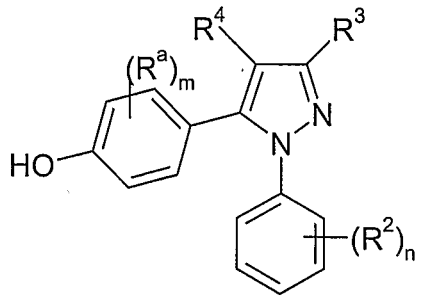
Compounds of formula I in which R^a, R^2, R^3, R^4, m and n are as previously defined and R^1 represents a group $R^5S(O)_2NH$ may be prepared by reacting a compound of formula II



II

in which R^a, R^2, R^3, R^4, m and n are as previously defined with a sulphonating agent of formula R^5SO_2L in which R^5 is as previously defined and L represents a leaving group, for example chloro, in an inert solvent, for example dichloromethane, in the presence of a base, for example triethylamine, at a temperature in the range of -25°C to 150°C.

Compounds of formula I in which R^1 represents a) a C_{1-3}alkoxy group substituted by one or more fluoro or C_{4-6}alkoxy group optionally substituted by one or more fluoro or b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, or c) a group $R^5S(O)_2O$ may be prepared by reacting a compound of formula III



III

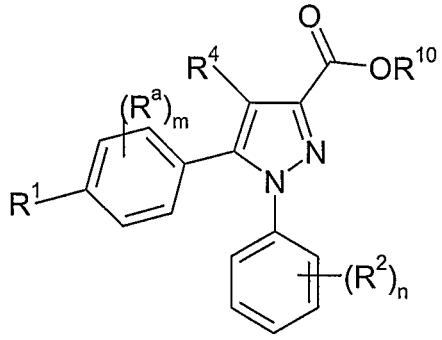
in which R^a, R^2, R^3, R^4, m and n are as previously defined with either

a) an alkylating agent of formula R^9X in which R^9 represents a C_{1-3}alkyl group substituted by one or more fluoro or C_{4-6}alkyl group optionally substituted by one or more fluoro and X represents a leaving group, for example chloro, bromo or iodo, in an inert solvent, for example acetone, in the presence of a base, for example potassium carbonate, at a temperature in the range of -25°C to 150°C; or

b) an alkylating agent of formula R^9X in which R^9 represents a group of formula phenyl$(CH_2)_p$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, and X represents a leaving group, for example chloro, bromo or iodo, in an inert solvent, for example acetone, in the presence of a base, for example potassium carbonate, at a temperature in the range of -25°C to 150°C; or

c) a sulphonating agent of formula R^5SO_2L in which R^5 is as previously defined and L represents a leaving group, for example chloro, in an inert solvent, for example dichloromethane, in the presence of a base, for example triethylamine, at a temperature in the range of -25°C to 150°C; respectively.

Compounds of formula I in which R^a, R^1, R^2, R^4, m and n are as previously defined and R^3 represents a group X-Y-NR^7R^8 in which X is CO , Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group and R^7 and R^8 are as previously defined may also be prepared by reacting a compound of formula IV



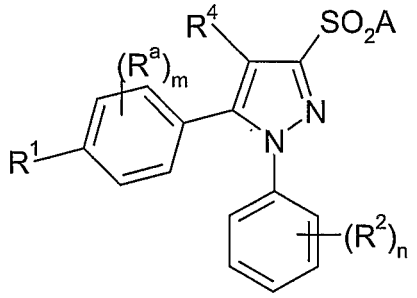
IV

in which R^a, R^1, R^2, R^4, m and n are as previously defined and R^{10} represents a C_{1-6}alkyl group with a compound of formula V

$R^7R^8YNH_2$ V

in which Y, R^7 and R^8 are as previously defined or a salt thereof in an inert solvent, for example toluene, in the presence of a Lewis acid, for example trimethylaluminium, at a temperature in the range of -25°C to 150°C;

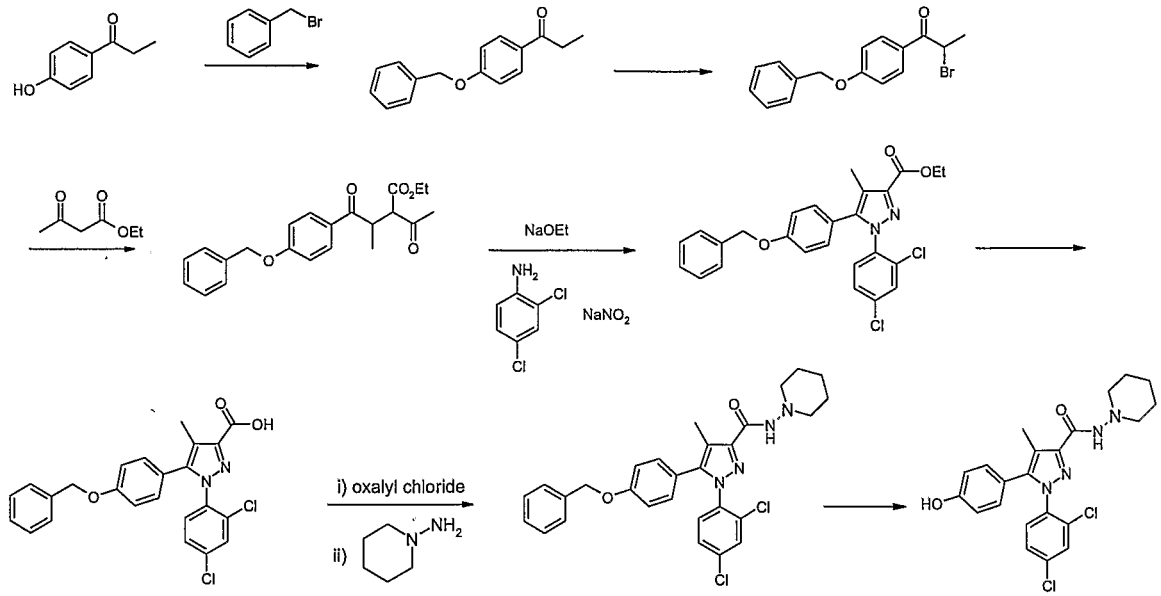
Compounds of formula I R^3 represents a group X-Y-NR^7R^8 in which X is SO_2, Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group and R^7 and R^8 are as previously defined may also be prepared by reacting a compound of formula VI



VI

in which R^a, R^1, R^2, R^4, m and n are as previously defined and A represents a leaving group, for example halo eg chloro, with a compound of formula V in which Y, R^7 and R^8 are as previously defined or a salt thereof in an inert solvent, for example THF ordichloromethane in the presence of a base, for example potassium carbonate, triethylamine or pyridine, at a temperature in the range of -25°C to 150°C.

Compounds of formula III, IV and VI may be prepared by methods analogous to the following method.



Certain intermediate compounds are believed to be novel and form part of the present invention. It will be appreciated by those skilled in the art that during the reaction sequence certain functional groups will require protection followed by deprotection at an appropriate stage see "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient or a pharmaceutically acceptable addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight. Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically

acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention of weight gain (e.g., medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, anorexia, bulimia and compulsive), cravings (for drugs, tobacco, alcohol, any appetizing macronutrients or non-essential food items), for the treatment of psychiatric disorders such as psychotic and/or mood disorders, schizophrenia and schizo-affective disorder, bipolar disorders, anxiety, anxio-depressive disorders, depression, mania, obsessive-compulsive disorders, impulse control disorders (e.g., Gilles de la Tourette's syndrome), attention disorders like ADD/ADHD, stress, and neurological disorders such as dementia and cognitive and/or memory dysfunction (e.g., amnesia, Alzheimer's disease, Pick's dementia, dementia of ageing, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild dementia of ageing), neurological and/or neurodegenerative disorders (e.g. Multiple Sclerosis, Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease), demyelinisation-related disorders, neuroinflammatory disorders (e.g., Guillain-Barré syndrome).

The compounds are also potentially useful for the prevention or treatment of dependence and addictive disorders and behaviours (e.g., alcohol and/or drug abuse, pathological gambling, kleptomania), drug withdrawal disorders (e.g., alcohol withdrawal with or without perceptual disturbances; alcohol withdrawal delirium; amphetamine withdrawal; cocaine withdrawal; nicotine withdrawal; opioid withdrawal; sedative, hypnotic or anxiolytic withdrawal with or without perceptual disturbances; sedative, hypnotic or anxiolytic withdrawal delirium; and withdrawal symptoms due to other substances), alcohol and/or drug-induced mood, anxiety and/or sleep disorder with onset during withdrawal, and alcohol and/or drug relapse.

The compounds are also potentially useful for the prevention or treatment of neurological dysfunctions such as dystonias, dyskinesias, akathisia, tremor and spasticity, treatment of spinal cord injury, neuropathy, migraine, vigilance disorders, sleep disorders (e.g.,

disturbed sleep architecture, sleep apnea, obstructive sleep apnea, sleep apnea syndrome), pain disorders, cranial trauma.

The compounds are also potentially useful for the treatment of immune, cardiovascular disorders (e.g. atherosclerosis, arteriosclerosis, angina pectoris, abnormal heart rythms, and arrythmias, congestive heart failure, coronary artery disease, heart disease, hypertension, prevention and treatment of left ventricular hypertrophy, myocardial infarction, transient ischaemic attack, peripheral vascular disease, systemic inflammation of the vasculature, septic chock, stroke, cerebral apoplexy, cerebral infarction, cerebral ischaemia, cerebral thrombosis, cerebral embolism, cerebral hemorrhagia, metabolic disorders (e.g. conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, diabetes mellitus, dyslipidemia, fatty liver, gout, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, hyperuricacidemia, impaired glucose tolerance, impaired fasting glucose, insulin resistance, insulin resistance syndrome, metabolic syndrome, syndrome X, obesity-hypoventilation syndrome (Pickwickian syndrome), type I diabetes, type II diabetes, low HDL- and/or high LDL-cholesterol levels, low adiponectin levels), reproductive and endocrine disorders (e.g. treatment of hypogonadism in males, treatment of infertility or as contraceptive, menstrual abnormalities/emmeniopathy, polycystic ovarian disease, sexual and reproductive dysfunction in women and men (erectile dysfunction), GH-deficient subjects, hirsutism in females, normal variant short stature) and diseases related to the respiratory (e.g. asthma and chronic obstructive pulmonary disease) and gastrointestinal systems (e.g. dysfunction of gastrointestinal motility or intestinal propulsion, diarrhea, emesis, nausea, gallbladder disease, cholelithiasis, obesity-related gastro-esophageal reflux, ulcers).

The compounds are also potentially useful as agents in treatment of dermatological disorders, cancers (e.g. colon, rectum, prostate, breast, ovary, endometrium, cervix, gallbladder, bile duct), craniopharyngioma, Prader-Willi syndrome, Turner syndrome, Frohlich's syndrome, glaucoma, infectious diseases, urinary tract disorders and inflammatory disorders (e.g. arthritis deformans, inflammation, inflammatory sequelae of viral encephalitis, osteoarthritis) and orthopedic disorders. The compounds are also potentially useful as agents in treatment of (esophageal) achalasia.

In another aspect the present invention provides a compound of formula I as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention of weight gain (e.g., medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, anorexia, bulimia and compulsive), cravings (for drugs, tobacco, alcohol, any appetizing macronutrients or non-essential food items), for the treatment of psychiatric disorders such as psychotic and/or mood disorders, schizophrenia and schizo-affective disorder, bipolar disorders, anxiety, anxio-depressive disorders, depression, mania, obsessive-compulsive disorders, impulse control disorders (e.g., Gilles de la Tourette's syndrome), attention disorders like ADD/ADHD, stress, and neurological disorders such as dementia and cognitive and/or memory dysfunction (e.g., amnesia, Alzheimer's disease, Pick's dementia, dementia of ageing, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild dementia of ageing), neurological and/or neurodegenerative disorders (e.g. Multiple Sclerosis, Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease), demyelinisation-related disorders, neuroinflammatory disorders (e.g., Guillain-Barré syndrome).

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of dependence and addictive disorders and behaviours (e.g., alcohol and/or drug abuse, pathological gambling, kleptomania), drug withdrawal disorders (e.g., alcohol withdrawal with or without perceptual disturbances; alcohol withdrawal delirium; amphetamine withdrawal; cocaine withdrawal; nicotine withdrawal; opioid withdrawal; sedative, hypnotic or anxiolytic withdrawal with or without perceptual disturbances; sedative, hypnotic or anxiolytic withdrawal delirium; and withdrawal symptoms due to other substances), alcohol and/or drug-induced mood, anxiety and/or sleep disorder with onset during withdrawal, and alcohol and/or drug relapse.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of neurological dysfunctions such as dystonias, dyskinesias, akathisia, tremor and spasticity, treatment of spinal cord injury, neuropathy, migraine, vigilance disorders, sleep disorders (e.g.,

disturbed sleep architecture, sleep apnea, obstructive sleep apnea, sleep apnea syndrome), pain disorders, cranial trauma.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of immune, cardiovascular disorders (e.g. atherosclerosis, arteriosclerosis, angina pectoris, abnormal heart rythms, and arrythmias, congestive heart failure, coronary artery disease, heart disease, hypertension, prevention and treatment of left ventricular hypertrophy, myocardial infarction, transient ischaemic attack, peripheral vascular disease, systemic inflammation of the vasculature, septic chock, stroke, cerebral apoplexy, cerebral infarction, cerebral ischaemia, cerebral thrombosis, cerebral embolism, cerebral hemorrhagia, metabolic disorders (e.g. conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, diabetes mellitus, dyslipidemia, fatty liver, gout, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, hyperuricacidemia, impaired glucose tolerance, impaired fasting glucose, insulin resistance, insulin resistance syndrome, metabolic syndrome, syndrome X, obesity-hypoventilation syndrome (Pickwickian syndrome), type I diabetes, type II diabetes, low HDL- and/or high LDL-cholesterol levels, low adiponectin levels), reproductive and endocrine disorders (e.g. treatment of hypogonadism in males, treatment of infertility or as contraceptive, menstrual abnormalities/emmeniopathy, polycystic ovarian disease, sexual and reproductive dysfunction in women and men (erectile dysfunction), GH-deficient subjects, hirsutism in females, normal variant short stature) and diseases related to the respiratory (e.g. asthma and chronic obstructive pulmonary disease) and gastrointestinal systems (e.g. dysfunction of gastrointestinal motility or intestinal propulsion, diarrhea, emesis, nausea, gallbladder disease, cholelithiasis, obesity-related gastro-esophageal reflux, ulcers).

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of dermatological disorders, cancers (e.g. colon, rectum, prostate, breast, ovary, endometrium, cervix, gallbladder, bile duct), craniopharyngioma, Prader-Willi syndrome, Turner syndrome, Frohlich's syndrome, glaucoma, infectious diseases, urinary tract disorders and inflammatory disoerders (e.g. arthritis deformans, inflammation, inflammatory sequelae of viral encephalitis, osteoarthritis) and orthopedic disorders.

In a still further aspect the present invention provides a method comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof for the prophylaxis or treatment of obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention of weight gain (e.g., medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, anorexia, bulimia and compulsive), cravings (for drugs, tobacco, alcohol, any appetizing macronutrients or non-essential food items), for the treatment of psychiatric disorders such as psychotic and/or mood disorders, schizophrenia and schizo-affective disorder, bipolar disorders, anxiety, anxio-depressive disorders, depression, mania, obsessive-compulsive disorders, impulse control disorders (e.g., Gilles de la Tourette's syndrome), attention disorders like ADD/ADHD, stress, and neurological disorders such as dementia and cognitive and/or memory dysfunction (e.g., amnesia, Alzheimer's disease, Pick´s dementia, dementia of ageing, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild dementia of ageing), neurological and/or neurodegenerative disorders (e.g. Multiple Sclerosis, Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease), demyelinisation-related disorders, neuroinflammatory disorders (e.g., Guillain-Barré syndrome).

In a still further aspect the present invention provides a method comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof for the prophylaxis or treatment of dependence and addictive disorders and behaviours (e.g., alcohol and/or drug abuse, pathological gambling, kleptomania), drug withdrawal disorders (e.g., alcohol withdrawal with or without perceptual disturbances; alcohol withdrawal delirium; amphetamine withdrawal; cocaine withdrawal; nicotine withdrawal; opioid withdrawal; sedative, hypnotic or anxiolytic withdrawal with or without perceptual disturbances; sedative, hypnotic or anxiolytic withdrawal delirium; and withdrawal symptoms due to other substances), alcohol and/or drug-induced mood, anxiety and/or sleep disorder with onset during withdrawal, and alcohol and/or drug relapse.

In a still further aspect the present invention provides a method comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof for the prophylaxis or treatment of neurological dysfunctions such as dystonias, dyskinesias, akathisia, tremor and spasticity, treatment of spinal cord injury, neuropathy,

migraine, vigilance disorders, sleep disorders (e.g., disturbed sleep architecture, sleep apnea, obstructive sleep apnea, sleep apnea syndrome), pain disorders, cranial trauma.

In a still further aspect the present invention provides a method comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof for the prophylaxis or treatment of immune, cardiovascular disorders (e.g. atherosclerosis, arteriosclerosis, angina pectoris, abnormal heart rythms, and arrythmias, congestive heart failure, coronary artery disease, heart disease, hypertension, prevention and treatment of left ventricular hypertrophy, myocardial infarction, transient ischaemic attack, peripheral vascular disease, systemic inflammation of the vasculature, septic chock, stroke, cerebral apoplexy, cerebral infarction, cerebral ischaemia, cerebral thrombosis, cerebral embolism, cerebral hemorrhagia, metabolic disorders (e.g. conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, diabetes mellitus, dyslipidemia, fatty liver, gout, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, hyperuricacidemia, impaired glucose tolerance, impaired fasting glucose, insulin resistance, insulin resistance syndrome, metabolic syndrome, syndrome X, obesity-hypoventilation syndrome (Pickwickian syndrome), type I diabetes, type II diabetes, low HDL- and/or high LDL-cholesterol levels, low adiponectin levels), reproductive and endocrine disorders (e.g. treatment of hypogonadism in males, treatment of infertility or as contraceptive, menstrual abnormalities/emmeniopathy, polycystic ovarian disease, sexual and reproductive dysfunction in women and men (erectile dysfunction), GH-deficient subjects, hirsutism in females, normal variant short stature) and diseases related to the respiratory (e.g. asthma and chronic obstructive pulmonary disease) and gastrointestinal systems (e.g. dysfunction of gastrointestinal motility or intestinal propulsion, diarrhea, emesis, nausea, gallbladder disease, cholelithiasis, obesity-related gastro-esophageal reflux, ulcers).

In a still further aspect the present invention provides a method comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof for the prophylaxis or treatment of dermatological disorders, cancers (e.g. colon, rectum, prostate, breast, ovary, endometrium, cervix, gallbladder, bile duct), craniopharyngioma, Prader-Willi syndrome, Turner syndrome, Frohlich's syndrome, glaucoma, infectious diseases, urinary tract disorders and inflammatory disorders (e.g.

arthritis deformans, inflammation, inflammatory sequelae of viral encephalitis, osteoarthritis) and orthopedic disorders..

The compounds of the present invention are particulary suitable for the treatment of obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention or reversal of weight gain (e.g., rebound, medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, anorexia, bulimia and compulsive), cravings (for drugs, tobacco, alcohol, any appetizing macronutrients or non-essential food items).

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders(e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight that normally accompanies the cessation of smoking.

In another aspect the present invention provides a compound of formula I as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases

related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

The compounds of the present invention are particulary suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

The compounds of the present invention may also be used to prevent or reverse medication-induced weight gain, e.g. weight gain caused by antipsychotic (neuroleptic) treatment(s).The compounds of the present invention may also be used to prevent or reverse weight gain associated with smoking cessation

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of obesity such as other anti-obesity drugs, that affect energy expenditure, glycolysis, gluconeogenesis, glucogenolysis, lipolysis, lipogenesis, fat absorption, fat storage, fat excretion, hunger and/or satiety and/or craving mechanisms, appetite/motivation, food intake, or G-I motility.

The compounds of the invention may further be combined with another therapeutic agent that is useful in the treatment of disorders associated with obesity such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes, sleep apnea, asthma, heart disorders,

atherosclerosis, macro and micro vascular diseases, liver steatosis, cancer, joint disorders, and gallbladder disorders. For example, a compound of the present invention may be used in combination with a another therapeutic agent that lowers blood pressure or that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of obesity and its associated complications the metabolic syndrome and type 2 diabetes, these include biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors).

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt thereof may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile acid binding resin.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor;

a cholesterol absorption antagonist;

a MTP (microsomal transfer protein) inhibitor ;

a nicotinic acid derivative, including slow release and combination products;

a phytosterol compound ;

probucol;

an anti-coagulant;

an omega-3 fatty acid ;

another anti-obesity compound for example sibutramine, phentermine, orlistat, bupropion, ephedrine, thyroxine;

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a melanin concentrating hormone (MCH) modulator;

an NPY receptor modulator;

an orexin receptor modulator;

a phosphoinositide-dependent protein kinase (PDK) modulator; or

modulators of nuclear receptors for example LXR, FXR, RXR, GR, ERRα, β, PPARα, β, γ and RORalpha;

a monoamine transmission-modulating agent, for example a selective serotonin reuptake inhibitor (SSRI), a noradrenaline reuptake inhibitor (NARI), a noradrenaline-serotonin reuptake inhibitor (SNRI), a monoamine oxidase inhibitor (MAOI), a tricyclic

antidepressive agent (TCA), a noradrenergic and specific serotonergic antidepressant (NaSSA);

an antipsychotic agent for example olanzapine and clozapine;

a serotonin receptor modulator;

a leptin/leptin receptor modulator;

a ghrelin/ghrelin receptor modulator;

a DPP-IV inhibitor;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of very low calorie diets (VLCD) or low-calorie diets (LCD).

Therefore in an additional feature of the invention, there is provided a method for the treatment of obesity and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of obesity and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt,

solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatohepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

It will be understood that there are medically accepted definitions of obesity and being overweight. A patient may be identified by, for example, measuring body mass index (BMI), which is calculated by dividing weight in kilograms by height in metres squared, and comparing the result with the definitions.

Pharmacological Activity

Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is demonstrable in methods described in Devane et al , Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively the assay may be performed as follows.

10μg of membranes prepared from cells stably transfected with the CB1 gene were suspended in 200μl of 100mM NaCl, 5mM $MgCl_2$, 1mM EDTA, 50mM HEPES (pH 7.4), 1mM DTT, 0.1% BSA and 100μM GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and 0.1μCi [^{35}S]-GTPγS. The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4),

5mM $MgCl_2$, 50mM NaCl). Filters were then covered with scintilant and counted for the amount of [^{35}S]-GTPγS retained by the filter.

Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and 100% activity respectively. At various concentrations of novel ligand, activity is calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation y=A+((B-A)/1+((C/x) ÙD)) and the IC50 value determined as the concentration required to give half maximal inhibition of GTPγS binding under the conditions used.

The compounds of the present invention are active at the CB1 receptor (IC50 <1 micromolar). Most preferred compounds have IC50 <200 nanomolar. For example the IC50 of Example 10 is 6.0nM and Example 11is 6.4nM.

The compounds of the invention are believed to be selective CB1 antagonists or inverse agonists. The potency, selectivity profile and side effect propensity may limit the clinical usefulness of hitherto known compounds with alleged CB1 antagonistic/inverse agonistic properties. In this regard, preclinical evaluation of compounds of the present invention in models of gastrointestinal and/or cardiovascular function indicates that they offer significant advantages compared to representative reference CB1 antagonist/inverse agonist agents.

The compounds of the present invention may provide additional benefits in terms of potency, selectivity profile, bioavailability, half-life in plasma, blood brain permeability, plasma protein binding (for example higher free fraction of drug) or solubility compared to representative reference CB1 antagonists/inverse agonist agents.

The utility of the compounds of the present invention in the treatment of obesity and related conditions is demonstrated by a decrease in body weight in cafeteria diet-induced obese mice. Female C57Bl/6J mice were given ad libitum access to calorie-dense 'cafeteria' diet (soft chocolate/cocoa-type pastry, chocolate, fatty cheese and nougat) and standard lab chow for 8-10weeks. Compounds to be tested were then administered systemically (iv, ip, sc or po) once daily for a minimum of 5 days, and the body weights of the mice monitored on a daily basis. Simultaneous assessment of adiposity was carried by means of DEXA imaging at baseline and termination of the study. Blood sampling was also carried out to assay changes in obesity-related plasma markers.

Examples

Abbreviations

AcOH	acetic acid
DCM	dichloromethane
DMF	dimethylformamide
DEA	diethylamine
DIEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
EtOAc	ethyl acetate
Et_3N	triethylamine
Ex or EX	Example
LiHMDS	lithium hexamethyldisilazide
MeOH	methanol
MeCN	acetnitrile
rt or RT	room temperature
TEA	triethylamine
THF	tetrahydrofuran
t	triplet
s	singlet
d	doublet
q	quartet
qvint	quintet
m	multiplet
br	broad
bs	broad singlet
dm	doublet of multiplet
bt	broad triplet
dd	doublet of doublet

General Experimental Procedures

Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass LCZ single quadrupole mass spectrometer both equipped with a pneumatically assisted electrospray interface (LC-MS). ^1H NMR measurements were performed on either a

Varian Mercury 300 or a Varian Inova 500, operating at ^1H frequencies of 300 and 500 MHz respectively. Chemical shifts are given in ppm with $CDCl_3$ as internal standard. $CDCl_3$ is used as the solvent for NMR unless otherwise stated. Purification was performed on a semipreparative HPLC (High Performance Liquid Chromatography) with a mass triggered fraction collector, Shimadzu QP 8000 single quadrupole mass spectrometer equipped with 19 x 100 mm C8 column. The mobile phase used was, if nothing else is stated, acetonitrile and buffer (0.1 M ammonium acetate:acetonitrile 95:5).
For isolation of isomers, a Kromasil CN E9344 (250 x 20 mm i.d.) column was used. Heptane:ethyl acetate:DEA 95:5:0.1 was used as mobile phase (1 ml/min). Fraction collection was guided using a UV-detector (330 nm).

Typical HPLC-parameters for purity analysis:

HPLC-system: Agilent 1100

Column: Zorbax Eclipse XDB-C8 150x4.6 mm

Time of analysis: 15 min

Flow: 1.5 ml/min

Mobilphase: A: water, 5% MeOH

B: MeOH

Temperature: 40 °C

Detector: Uv 240nm

Examples of the Invention

Example 1

Step A 1-(4-Benzyloxyphenyl)propan-1-one

4-Hydroxypropiophenone (15.0 g, 0.10 mol) was dissolved in acetone (200 ml) together with potassium carbonate (13.8 g, 0.10 mol). Benzyl bromide (17.1 g, 0.10 mol) was added and the reaction mixture heated at reflux overnight. After cooling to room temperature the mixture was filtered and concentrated on the rotary evaporator to afford 24.0 g (100%) of the title compound as a white solid

Step B 1-(4-Benzyloxyphenyl)-2-bromopropan-1-one

1-(4-Benzyloxyphenyl)propan-1-one (4.80 g, 20.0 mmol) was suspended in acetic acid (25 ml) and cooled to 0 °C. Bromine (3.20 g, 20.0 mmol) was added dropwise and the reaction mixture stirred two hours at room temperature at which point the reaction mixture was a

clear, yellow solution. After cooling, water (100 ml) was added and the product extracted with ether (2 x 100 ml). The combined organic extracts were washed with water, sodium hydrogen carbonate and brine. The organic phase was dried (Na_2SO_4), filtered and evaporated leaving the title compound as a pale yellow solid (6.17 g, 97%).

Step C 2-[2-(4-Benzyloxy-phenyl)-2-oxo-ethyl]-3-oxo-butyric acid ethyl ester

A solution of sodium ethoxide was generated from sodium metal (0.53 g, 23.0 mmol) in 30 ml abs. ethanol. To this solution was added ethyl acetoacetate (3.00 g, 23.0 mmol) at 0 °C. After 30 min. this solution was added to a solution of 1-(4-benzyloxyphenyl)-2-bromo-propan-1-one (6.17 g, 19.0 mmol) in ethanol : toluene (30 : 15 ml) and the reaction mixture stirred overnight. Acidic work-up with 1 M HCl, extraction with ethyl acetate (3 x), washing with brine, drying (Na_2SO_4), filtering and evaporation left a crude product purified by flash chromatography (hexane : EtOAc 95 : 5 – 70 : 30) affording 5.18 g of the title compound as a pale yellow oil.

Step D 5-(4-Benzyloxyphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid

A solution of sodium ethoxide was generated from sodium metal (0.19 g, 8.26 mmol) in 20 ml abs. ethanol. To this solution was added 2-[2-(4-benzyloxyphenyl)-2-oxo-ethyl]-3-oxo-butyric acid ethyl ester (2.13 g, 6.00 mmol) and the reaction mixture stirred at room temperature for 30 min. A previously prepared solution of 2,4-dichlorophenyldiazonium chloride (prepared from 2,4-dichloroaniline (1.19 g, 7.30 mmol) in 3 ml 24% HCl and sodium nitrite (0.52 g, 7.50 mmol) in 3 ml water at 0 °C) was added in 5 portions keeping the temperature below 5 °C. After stirring at room temperature for 2.5 hours water was added, and the product extracted with EtOAc (3 x). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was dissolved in ethanol (40 ml) and sodium hydroxide (0.80 g, 20.0 mmol) in 10 ml of water was added. After 2 hours boiling under reflux the reaction mixture was cooled, acidified with HCl and the product extracted with EtOAc (3 x). After washing, drying (Na_2SO_4), filtration and concentration, the residue was purified by flash chromtography (hexane : EtOAc 70:30 – 50:50) affording 1.84 g (68%) of the title compound as a pale yellow solid.

Step E 5-(4-Benzyloxyphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide

5-(4-Benzyloxyphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid (1.84 g, 4.07 mmol) was suspended in dichloromethane and a few drops of DMF added followed by the addition of oxalyl chloride (1.03 g, 8.14 mmol). The reaction mixture was refluxed for two hours. After cooling to room temperature, the solvent was removed and the crude acid chloride redissolved in dichloromethane and cooled to 0 °C. Triethylamine (1.15 ml, 8.20 mmol) was added followed by 1-aminopiperidine (0.5 ml, 4.50 mmol). The cooling bath was removed and the reaction mixture stirred at room temperature for 2 hours. Water was added and the product extracted with dichloromethane (3 x). The combined extracts were dried (Na_2SO_4), filtered and evaporated. Flash chromatography (hexane : EtOAc 80 : 20 – 70 : 30) afforded 1.13 g (52%) of the title compound as a solid.

Step F 1-(2,4-Dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-yl amide

5-(4-Benzyloxyphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide (1.00 g, 1.87 mmol) was dissolved in 25 ml of abs. ethanol together with 100 mg of palladium on charcoal (10% Pd). The reaction was hydrogenated with a balloon overnight. Filtration, concentration and flash chromatography (hexane : EtOAc 50 : 50 – EtOAc) afforded 0.83 g (100%) of the title compound as a solid.

Step G Propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)2*H*-pyrazol-3-yl]-phenyl ester

1-(2,4-Dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-yl amide (222 mg, 0.50 mmol) was dissolved in dichloromethane (10 ml) and triethylamine (0.07 ml, 0.50 mmol) was added. Propanesulfonyl chloride (71 mg, 0.50 mmol) was added at 0 °C, the cooling bath removed and the reaction stirred at room temperature for 2 hours. Water was added and the product was extracted with dichloromethane, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (hexane : EtOAc 70 : 30 – 50 :50) afforded a product that was recrystallised from hexane : EtOAc to give 135 mg (49%) of the the title compound as a white solid m.p. 190 °C.

^{1}H NMR($CDCl_3$): δ 7.66 (1H, broad s), 7.44-7.17 (7 H, m), 3.25 (2H, t), 2.90 (4H, m), 2.39 (3H, s), 2.09-1.97 (2H, m), 1.78 (4H, m), 1.45 (2 H, m), 1.17 (3H, t)

MS m/z 573 (M+Na)

Example 2

1-(2,4-Dichlorophenyl)-4-methyl-5-[4-(4,4,4-trifluorobutoxy)-phenyl]-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide

1-(2,4-Dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-yl amide from **Ex 1, Step F** (250 mg, 0.56 mmol) was dissolved in acetone (10 ml) and potassium carbonate (77 mg, 0.56 mmol) was added followed by 1-iodo-4,4,4-trifluorobutane (140 mg, 0.56 mmol). The reaction mixture was boiled under reflux overnight, concentrated and purified by flash chromatography (hexane : EtOAc 70 : 30 – 60 : 40) afforded 130 mg (42%) of a white solid that was triturated with hexane : EtOAc 95 : 5 and filtered.

^{1}H NMR($CDCl_3$): δ 7.63 (1H, broad s), 7.43 (1H, m), 7.30 (2H, m), 7.10-7.00 (2H, m), 6.85-6.78 (2H, m), 4.05 (2H, t), 2.90 (4H, m), 2.40-2.19 (5H, s and m), 2.15-1.97 (2H, m), 1.78 (4H, m), 1.45 (2 H, m)

MS m/z 577 (M+Na). HPLC: 98.4%

Example 3

Butane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]-phenyl ester

1-(2,4-Dichlorophenyl)-5-(4-hydroxy-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-yl amide, prepared as in **Ex 1, Step F** (350 mg, 0.78 mmol) was dissolved in dichloromethane (10 ml) and triethylamine (0.11 ml, 0.78 mmol) was added. Butanesulfonyl chloride (0.12 g, 0.78 mmol) was added at 0 °C, the cooling bath removed and the reaction stirred at room temperature overnight. Water was added, the product extracted with dichloromethane, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (hexane : EtOAc 70 : 30 – 50 :50) afforded a product that was recrystallised from hexane : EtOAc to give 200 mg (45%) of the the title compound as a solid.

^{1}H NMR($CDCl_3$): δ 7.48-7.19 (8H, m), 3.29 (2H, m), 2.96 (4H, m), 2.41 (3H, s), 2.09-1.97 (2H, m), 1.81 (4H, m), 1.64-1.50 (4 H, m), 1.02 (3H, t)

Example 4

Propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(morpholin-4-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester

Step A 5-(4-Benzyloxyphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide

To a solution of 5-(4-benzyloxyphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid, prepared as in **Ex 1, Step D** (1.18 g, 2.6 mmol) in 25 ml CH_2Cl_2 was added 2 drops of DMF followed by oxalyl chloride (0.44 ml, 5.2 mmol). The mixture was boiled under reflux for 2 hours, cooled to room temperature and evaporated to dryness. The residue was dissolved in 25 ml CH_2Cl_2 and cooled to 0°C. Triethylamine (0.73 ml, 5.2 mmol) was added followed by 1-aminopiperidine (0.28 ml, 2.9 mmol) and the mixture was stirred at room temperature for 3 hours. Water (100 ml) was added and the mixture was extracted with CH_2Cl_2 (3x50 ml), dried (Na_2SO_4), filtered and concentrated. Flash chromatography (silica, hexane:EtOAc 1:2, EtOAc) afforded 215 mg (15%) of the title compound as a white solid.

Step B 1-(2,4-Dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide

5-(4-Benzyloxyphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide (215 mg, 0.40 mmol) was dissolved in 20 ml CH_2Cl_2 and cooled to 0°C. Boron tribromide (78 µl, 0.80 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 2.5 hours. Water (50 ml) was added and the solution extracted with EtOAc (3x50 ml). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Flash chromatography (silica, hexane:EtOAc 1:2, EtOAc) afforded 180 mg (99%) of the title compound as a white solid.

Step C Propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(morpholin-4-ylcarbamoyl)-2*H*-pyrazol-3-yl]-phenyl ester

A solution of 1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide (180 mg, 0.40 mmol) in 10 ml CH_2Cl_2 was cooled to 0°C. Triethylamine (56 µl, 0.40 mmol) was added followed by 1-propanesulfonyl chloride (45 µl, 0.40 mmol) and the reaction mixture was stirred at room temperature for 5 hours.

Water was added and the mixture was extracted with CH_2Cl_2 (3x20 ml), dried (Na_2SO_4), filtered and concentrated. Flash chromatography (silica, hexane:EtOAc 1:2) afforded 82 mg (46%) of the title compound as a white solid.

^{1}H NMR (CDCl3): δ 7.7 (1H, s), 7.5-7.4 (1H, m), 7.4-7.1 (6H, m), 3.9-3.8 (4H, m), 3.3-3.2 (2H, m), 3.0-2.9 (4H, m), 2.4 (3H, s), 2.1-1.9 (2H, m), 1.2 (3H, t).

MS m/z 576 (M+Na). HPLC: 98.0%.

Example 5

3,3,3-Trifluoropropane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester

Step A 1-(2,4-Dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-yl amide

5-(4-Benzyloxyphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide, prepared as in **Ex. 1, Step E** (330 mg, 0.62 mmol) was dissolved in 20 ml CH_2Cl_2 and cooled to 0°C. Boron tribromide (120 µl, 1.24 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 1 hour. Water (50 ml) was added and the solution extracted with EtOAc (3x20 ml). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Flash chromatography (silica, hexane:EtOAc 1:3, EtOAc) afforded 130 mg (47%) of the title compound as a white solid.

Step B 3,3,3-Trifluoropropane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester

A solution of 1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-yl amide,(130 mg, 0.30 mmol) in 10 ml CH_2Cl_2 was cooled to 0°C. Triethylamine (42 µl, 0.30 mmol) was added followed by 3,3,3-trifluoropropane-1-sulfonyl chloride (59 mg, 0.30 mmol), purchased from Manchester Organics (but may also be prepared in an analogous manner to the method described in WO200010968 for 4,4,4-trifluorobutane-1-sulfonyl chloride), and the reaction mixture was stirred at room temperature for 2 hours, Water was added and the mixture was extracted with CH_2Cl_2 (3x20 ml), dried (Na_2SO_4), filtered and concentrated. Flash chromatography (silica, hexane:EtOAc 7:3, 6:4) afforded 150 mg (82%) of the title compound as a white solid m.p. 160 °C.

^{1}H NMR ($CDCl_3$): δ 7.7 (1H, broad s), 7.5-7.2 (7H, m), 3.6-3.5 (2H, m), 3.0-2.7 (6H, m), 2.4 (3H, s), 1.9-1.7 (4H, m), 1.6-1.4 (2H, m).

MS m/z 628 (M+Na). HPLC: 92.5%.

Example 6

4,4,4-Trifluorobutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester

1-(2,4-Dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-yl amide, prepared as in **Ex 5, Step A** (0.49 g, 1.20 mmol) was dissolved in dichloromethane (20 ml), cooled to 0 ^oC and triethylamine (0.67 ml, 4.8 mmol) added followed by 4,4,4-trifluorobutane-1-sulfonyl chloride, prepared as described in WO200010968, (0.38 g, 1.80 mmol). The reaction mixture was stirred at room temperature overnight. Water was added, the product extracted with dichloromethane, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (hexane : EtOAc 1 : 1 – EtOAc) followed by recrystallisation (hexane : EtOAc) afforded 0.32 g (43%) of the title compound as a colorless solid.

^{1}H NMR($CDCl_3$): δ 7.80 (1H, broad s), 7.50-7.19 (7H, m), 3.40 (2H, m), 3.05-2.90 (4H, m), 2.50-2.20 (7H, s and m), 1.92-1.70 (4H, m), 1.57-1.40 (2H, m).

MS m/z 641 (M+Na)

HPLC: 96.5%

Example 7

Propane-1-sulfonic acid-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]-2,6-difluorophenyl ester

Step A 1-(4-Benzyloxy-3,5-difluorophenyl)-propane-1-one

1-(3,5-Difluoro-4-hydroxyphenyl)propane-1-one (5.00 g, 26.9 mmol) was dissolved in acetone (100 ml) together with potassium carbonate (3.90 g, 28.2 mmol). Benzyl bromide (4.82 g, 28.2 mmol) was added and the reaction mixture was boiled under reflux overnight. After cooling to room temperature the mixture was filtered and concentrated on a rotary evaporator to afford 7.43 g (100%) of the title compound as a white solid.

Step B 1-(4-Benzyloxy-3,5-difluorophenyl)-2-bromopropan-1-one

1-(4-Benzyloxy-3,5-difluorophenyl)propane-1-one (7.43 g, 26.9 mmol) was suspended in acetic acid (35 ml). Bromine (4.28 g, 26.8 mmol) was added dropwise and the reaction mixture stirred two hours at room temperature at which point the reaction mixture was a clear, yellow solution. After cooling, ice-water (100 ml) was added and the product extracted with ether (2 x 100 ml). The combined organic extracts were washed with water, sodium hydrogen carbonate solution and brine. The organic phase was dried (Na_2SO_4), filtered and evaporated leaving 9.30 g (98%) of the title compound as a pale yellow oil.

Step C 2-Acetyl-4-(4-benzyloxy-3,5-difluorophenyl)-3-methyl-4-oxobutyric acid ethyl ester

A solution of sodium ethoxide was generated from sodium metal (0.74 g, 32.0 mmol) in 40 ml absolute ethanol. To this solution was added ethyl acetoacetate (4.16 g, 32.0 mmol) at 0 °C. After 30 min. this solution was added to a solution of 1-(4-benzyloxy-3,5-difluorophenyl)-2-bromopropan-1-one (9.30 g, 26.2 mmol) in ethanol : toluene (40 : 20 ml) and the reaction mixture stirred overnight. Acidic work-up with 1 M HCl, extraction with ethyl acetate (3 x), washing with brine, drying (Na_2SO_4), filtering and evaporation left a crude product purified by flash chromatography (hexane : EtOAc 95 : 5 – 70 : 30) affording 6.95 g (66%) of the title compound as an oil.

Step D 5-(4-Benzyloxy-3,5-difluorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid

A solution of sodium ethoxide was generated from sodium metal (0.53 g, 22.0 mmol) in 60 ml absolute ethanol. To this solution was added 2-acetyl-4-(4-benzyloxy-3,5-difluorophenyl)-3-methyl-4-oxobutyric acid ethyl ester (6.95 g, 17.2 mmol) and the reaction mixture stirred at room temperature for 30 min. A previously prepared solution of 2,4-dichlorophenyldiazonium chloride (prepared from 2,4-dichloroaniline (3.39 g, 21.0 mmol) in 9 ml 24% HCl and sodium nitrite 1. (48 g, 21.0 mmol) in 3 ml water at 0 °C) was added in 5 portions keeping the temperature below 5 °C. After stirring at 0 °C for 2 hours the reaction mixture was allowed to reach room temperature and stirred overnight. Water was added, the product extracted with EtOAc (3 x). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated leaving 9.20 g of the crude ethyl ester as an oil.

The residue (9.20 g) was dissolved in ethanol (120 ml) and sodium hydroxide (2.30 g, 57.5 mmol) in 15 ml of water was added. After 2 hours of boiling under reflux the reaction mixture was cooled, acidified with HCl and the product extracted with EtOAc (3 x). After washing, drying (Na_2SO_4), filtration and concentration, the residue was purified by flash chromtography (hexane : EtOAc : AcOH 80:20:2 – hexane : EtOAc : AcOH 50:50:2) affording 5.46 g (65%, two steps) of the title compound as a solid.

Step E 5-(4-Benzyloxy-3,5-difluorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide

5-(4-Benzyloxy-3,5-difluorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid (5.46 g, 11.2 mmol) was suspended in dichloromethane (60 ml) and a few drops of DMF added followed by the addition of oxalyl chloride (4.70 ml, 55.8 mmol). The reaction mixture was boiled under reflux for 1.5 hours. After cooling to room temperature the solvent was removed and the crude acid chloride redissolved in dichloromethane, cooled to 0 °C, Et_3N (3.10 ml, 22.2 mmol) was added followed by 1-aminopiperidine (1.2 ml, 11.2 mmol). The cooling bath was removed and the reaction mixture stirred at room temperature overnight. Water was added and the product extracted with dichloromethane (3 x), the combined extracts dried (Na_2SO_4), filtered and evaporated. Flash chromatography (hexane : EtOAc 80 : 20 – 70 : 30) afforded 1.86 g (30%) of the title compound as a yellow solid.

Step F 5-(4-Hydroxy-3,5-difluorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide

5-(4-Benzyloxy-3,5-difluorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide (1.86 g, 3.25 mmol) was dissolved in 50 ml of dichloromethane and cooled to -78 °C. BBr_3 (0.60 ml, 6.50 mmol) was added slowly and the reaction mixture stirred at 0 °C for 30 min. Water was added and the product extracted with CH_2Cl_2 (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Flash chromatography (hexane : EtOAc 50 : 50) afforded 0.64 g (41%) of the title compound as a pale yellow solid.

Step G Propane-1-sulfonic acid-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]-2,6-difluorophenyl ester

5-(4-Hydroxy-3,5-difluorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide (0.64 g, 1.32 mmol) was dissolved in dichloromethane (20 ml), cooled to 0 °C and triethylamine (0.18 ml, 1.32 mmol) added followed by propanesulfonyl chloride (0.19 g, 1.31 mmol). The reaction mixture was stirred at room temperature overnight. Water was added, the product extracted with dichloromethane, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (hexane : EtOAc 70 : 30 – 50 : 50) afforded 410 mg (53%) of the title compound as pale yellow solid.

^{1}H NMR($CDCl_3$): δ 7.66 (1H, broad s), 7.60-7.24 (4 H, m), 6.97-6.78 (1H, m), 3.50-3.37 (2H, m), 3.02-2.80 (4H, m), 2.40 (3 H, s), 2.20-2.00 (2H, m), 1.92-2.72 (4 H, m), 1.60-1.40 (2 H, m), 1.08 (3H, t).

MS m/z 609 (M+Na). HPLC: 97.5%.

Example 8

Propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester

Step A 4-(4-Benzyloxyphenyl)-2,4-dioxobutyric acid ethyl ester

To a solution of LiHMDS (88 ml, 1M in THF) in ether (50 ml) under nitrogen at –78 °C was added during 1 hour a suspension of 1-(4-benzyloxyphenyl)ethanone (20 g, 88.4 mmol) dissolved in ether (150 ml) and THF (50 ml). The resulting mixture was stirred at -78 °C for 1 hour and then oxalic acid diethyl ester (14.2 g, 97.2 mmol) was added. The resulting mixture was slowly warmed to room temperature and then left overnight. The reaction mixture was diluted with pentane (90 ml) and the crude product precipitated as its lithium salt. The collected solid (27.2 g) was dried under vacuum and used directly in the next step.

Step B 5-(4-Benzyloxyphenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester

4-(4-Benzyloxyphenyl)-2,4-dioxobutyric acid ethyl ester (27.2 g, as Li salt from previous step) was suspended in ethanol (350 ml) and 2,4-dichlorophenylhydrazine (17.8 g, 83.3 mmol) was added. The reaction mixture was stirred overnight at room temperature. The solvent was then removed under reduced pressure and the residue was dissolved in acetic acid and the resulting mixture was refluxed for 24 h. The reaction mixture was diluted with

ethyl acetate (1L) and then washed with saturated $NaHCO_3$ (6x250 ml) and brine (100 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oil. The oil was purified by flash chromatography (SiO_2, 20% EtOAc in heptane). The product fraction was concentrated under reduced pressure and the remaining material was then further purified by recrystallisation (ethyl acetate/heptane) to give a white solid (19.6, 57% over 2 steps).

^{1}H-NMR ($CDCl_3$): δ 1.42 (t, 3H), 4.45 (q, 2H), 5.03 (s, 2H), 6.88 (d, 2H), 7.01 (s, 1H), 7.11 (d, 2H), 7.3-7.45 (m, 8H).

MS: 467 (M+1).

Step C 1-(2,4-Dichlorophenyl)-5-(4-hydroxyphenyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester

To a solution of 5-(4-benzyloxyphenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester (735 mg, 1.57 mmol) and $(CH_3)_2S$ (0.58 ml, 7.86 mmol) in dichloromethane (30 ml) under nitrogen was added BF_3-diethyl etherate (1.0 ml, 7.86 mmol) dropwise. The resulting mixture was stirred overnight at room temperature. More $(CH_3)_2S$ (0.58 ml, 7.86 mmol) and BF_3-diethyl etherate (1.0 ml, 7.86 mmol) was then added and the resulting mixture was stirred for another 3 days. The reaction mixture was diluted with dichloromethane to 80 ml and washed with water (3x30 ml) and brine (40 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white solid (573 mg, 96%). The crude material was used directly.

^{1}H-NMR ($CDCl_3$) : δ 1.41 (t, 3H), 4.44 (q, 2H), 6.74 (d, 2H), 7.00 (s, 1H), 7.06 (d, 2H), 7.3-7.45 (m, 3H). MS: 375 (M-1).

Step D 1-(2,4-Dichlorophenyl)-5-[4-(propane-1-sulfonyloxy)-phenyl]-1H-pyrazole-3-carboxylic acid ethyl ester

1-(2,4-Dichlorophenyl)-5-(4-hydroxyphenyl)-1*H*-pyrazole-3-carboxylic acid ethyl ester (510 mg, 1.35 mmol) was suspended in dichloromethane (20 ml) under nitrogen and triethylamine (0.75 ml, 5.4 mmol) was added. The resulting mixture was cooled to 0 °C and 1-propanesulfonyl chloride (0.30 ml, 2.7 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 hour. The reaction mixture was then diluted to 40 ml with dichloromethane and then washed with saturated $NaHCO_3$ (3x20 ml) and brine (20 ml).

The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oil (0.64 g, 98%). The crude material was used as such without further purification.
^{1}H-NMR ($CDCl_3$): δ 1.12 (t, 3H), 1.43 (t, 3H), 2.01 (m, 2H), 3.23 (m, 2H), 4.46 (q, 2H), 7.07 (s, 1H), 7.19-7.46 (m, 7H).
MS: 483 (M+1).

Step E Propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester

1-Aminopiperidine hydrochloride (36 mg, 0.26 mmol) was dissolved in toluene (1.0 ml) under nitrogen atmosphere. Trimethylaluminium (2 M in toluene, 0.17 ml) was added dropwise at room temperature. The resulting mixture was then stirred at room temperature for 40 minutes. This mixture was then added to a stirred suspension of 1-(2,4-dichlorophenyl)-5-[4-(propane-1-sulfonyloxy)phenyl]-1*H*-pyrazole-3-carboxylic acid ethyl ester (42 mg, 0.087 mmol) in DCM (1.0 ml) and the resulting mixture was heated at 60 °C overnight. The reaction was quenched by addition of water and then partitioned between water (20 ml) and DCM (20 ml). The organic layer was washed with water (3x10 ml) and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC, C8 column, 5-100% acetonitrile in water (buffer: 0.1 M ammonium acetate). The product fraction was diluted with ethyl acetate and washed with water several times. The organic layer was concentrated under reduced pressure and the residue was freeze-dried to give a white solid (26 mg, 55%).
^{1}H-NMR ($CDCl_3$): 1.11 (t, 3H), 1.43 (m, 2H), 1.76 (m, 4H), 2.00 (m, 2H), 2.85 (m, 4H), 3.22 (m, 2H), 7.11 (m, 1H), 7.20 (m, 4H), 7.37 (m, 2H), 7.49 (m, 1H).
MS: 537 (M+1).

Example 9

Propane-1-sulfonic acid 4-[4-bromo-2-(2,4-dichlorophenyl)-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester

Step A 4-Bromo-1-(2,4-dichlorophenyl)-5-[4-(propane-1-sulfonyloxy)phenyl]-1H-pyrazole-3-carboxylic acid ethyl ester

1-(2,4-Dichlorophenyl)-5-[4-(propane-1-sulfonyloxy)phenyl]-1H-pyrazole-3-carboxylic acid ethyl ester, prepared as in **Ex. 8, Step D** (597 mg, 1.23 mmol) was dissolved in

dichloromethane (15 ml) and bromine (0.06 ml, 1.23 mmol) in dichloromethane (1 ml) was added and the resulting mixture was stirred at room temperature overnight. Extra bromine (0.06 ml, 1.23 mmol) was added and the mixture was stirred for another 20 hours.

The reaction mixture was diluted to 80 ml with dichloromethane and was then washed with saturated $NaHCO_3$ (40 ml), 20% $Na_2S_2O_5$ (40 ml), saturated $NaHCO_3$ (2x40 ml) and brine (40 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an orange oil (0.598, 73%). The crude material was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 1.12 (t, 3H), 1.44 (t, 3H), 2.01 (m, 2H), 3.24 (m, 2H), 4.48 (q, 2H), 7.2-7.46 (m, 7H). MS: 561

Step B Propane-1-sulfonic acid 4-[4-bromo-2-(2,4-dichlorophenyl)-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester

This compound was prepared in a similar manner to that described in **Ex.8 Step E**. by reacting 4-bromo-1-(2,4-dichlorophenyl)-5-[4-(propane-1-sulfonyloxy)phenyl]-1*H*-pyrazole-3-carboxylic acid ethyl ester with 1-aminopiperidine hydrochloride to give 26mg of the title compound as a white solid. Yield: 25%

^{1}H-NMR ($CDCl_3$): 1.12 (t, 3H), 1.43 (m, 2H), 1.74 (m, 4H), 2.01 (m, 2H), 2.90 (m, 4H), 3.24 (m, 2H), 7.21-7.45 (m, 7H)

MS: 615.

Example 10

Methyl 1-{[(1-(2,4-dichlorophenyl)-4-methyl-5-{4[(propylsulfonyl)oxy]phenyl}-1*H*-pyrazol-3-yl)carbonyl]amino}cyclopentanecarboxylate

Step A Methyl 1-aminocyclopentanecarboxylate hydrochloride

Thionyl chloride (1.5 ml) was dissolved in methanol (15 ml) and poured over 1-aminocyclopentanecarboxylic acid (100 mg, 0.774 mmol). The mixture was refluxed 1 hour. The solvent was evaporated to give the product (107 mg, 77%).

^{1}H NMR (399.964 MHz) δ 9.00-8.60 (br, 3H), 3.79 (s, 3H), 2.23 (s, 4H), 2.14-2.00 (m, 2H), 1.90-1.76 (m, 2H).

Step B Methyl 1-({[5-[4-(benzyloxy)phenyl]-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl]carbonyl}amino)cyclopentanecarboxylate

A solution of 5-[4-benzyloxy)phenyl]-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-carboxylic acid, prepared as in **Ex.1, Step D** (59 mg, 0.130 mmol) in DCM (2 ml) was

mixed with a solution of oxalyl chloride (2 ml) in DCM (20 ml). One drop of DMF was added and the reaction continued at room temperature in the dark for1 hour. The solvent was evaporated, DCM (2 ml) was added and the acid chloride mixture added to a mixture of methyl 1-aminocyclopentanecarboxylate hydrochloride (23 mg, 0.130 mmol) in DCM (2 ml) and K_2CO_3 (aq, 10 wt%, 2 ml). The reaction was continued at room temperature for 3 hours. The phases were separated and the organic phase washed with water and dried over $MgSO_4$ to give the product (71 mg, 94 %).

^{1}H NMR (399.964 MHz) δ 7.43-7.23 (m, 9H), 7.06-7.00 (m, 2H), 6.93-6.87 (m, 2H), 5.02 (s, 2H), 3.75 (s, 3H), 2.40-2.30 (m, 2H), 2.34 (s, 3H), 2.14-2.04 (m, 2H), 1.87-1.77 (m, 4H).

MS *m/z* 578, 580, 582 $(M+H)^+$.

Step C Methyl 1-({[1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazol-3-yl]carbonyl}amino)cyclopentanecarboxylate

Boron trifluoride etherate (156 µl, 1.23 mmol) was added to a mixture of methyl 1-({[5-[4-(benzyloxy)phenyl]-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl]carbonyl}amino)cyclopentanecarboxylate (51 mg, 0.088 mmol) and dimethyl sulfide (90 µl, 1.23 mmol) in DCM (2 ml). The reaction was continued at room temperature in the dark for 46 hours. Water and DCM were added, the phases separated and the organic phase washed with water and dried over $MgSO_4$ (39 mg, 90%).

^{1}H NMR (399.964 MHz) δ 7.60-6.60 (m, 8H), 3.72 (s, 3H), 2.43-2.23 (m, 2H), 2.26 (s, 3H), 2.15-2.00 (m, 2H), 1.85-1.75 (m, 4H).

MS *m/z* 488, 490, 492 $(M+H)^+$.

Step D Methyl 1-{[(1-(2,4-dichlorophenyl)-4-methyl-5-{4[(propylsulfonyl)oxy]phenyl}-1*H*-pyrazol-3-yl)carbonyl]amino}cyclopentanecarboxylate.

TEA (100 µl) and then 1-propanesulfonyl chloride (30 µl, 0.268 mmol) were added to a mixture of methyl 1-({[1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazol-3-yl]carbonyl}amino)cyclopentanecarboxylate (39 mg, 0.080 mmol) in dry DCM (1.5 ml) at –78°C. The reaction was continued at –78°C under N_2(g) for 1.5 hours. Water and DCM were added and the temperature was raised to room temperature. The phases were separated and the orgainc phase washed with water and dried over $MgSO_4$. The product was purified by preparatory HPLC (kromasil C8 column, ammonium acetate (aq, 0.1

M):acetonitrile, product came at about 88% acetonitrile) to give the product as an almost white powder (17 mg, 35%).

^{1}H NMR (399.964 MHz) δ 7.45-7.39 (br, 1H), 7.32-7.28 (m, 2H), 7.27-7.19 (m, 3H), 7.18-7.12 (m, 2H), 3.76 (s, 3H), 3.26-3.20 (m, 2H), 2.40-2.30 (m, 2H), 2.35 (s, 3H), 2.15-2.05 (m, 2H), 2.05-1.95 (m, 2H), 1-88-1.78 (m, 4H), 1.12 (t, 3H).

HRMS Calcd for $[C_{27}H_{29}Cl_2N_3O_6S+H]^+$: 594.123. Found: 594.121.

Example 11

Carbonic acid 4-[2-(2,4-dichloro-phenyl)-4-methyl-5-(piperidine-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]-phenyl ester propyl ester

Carbonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidine-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]-phenyl ester propyl ester

1-(2,4-Dichloro-phenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-yl amide prepared as in Ex 1, Step F (0.44 g, 1.00 mmol) was dissolved in dichloromethane (10 ml) and triethylamine (0.28 ml, 2.24 mmol) was added. Propyl chloroformate (0.14 ml, 1.24 mmol) was added at 0 °C, and the reaction stirred for 40 min., concentrated and the product purified by flash chromatography (hexane : EtOAc 70 :30 – 50 : 50) to afford 345 mg (65%) of the title compound. Further purification by preparative HPLC gave 239 mg of the title compound.

^{1}H NMR($CDCl_3$): δ 7.71-7.18 (8H, m), 4.24 (2H, t), 2.93 (4H, m), 2.40 (3H, s), 1.78 (6H, m), 1.46 (2H, m), 1.03 (3H, t)

MS m/z 553 (M+Na)

HPLC: 94.15%

Example 12

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl thiophene-2-sulfonate

Thiophene-2-sulfonyl chloride (433 mg, 2.37 mmol) in DCM (2.5 ml) was added to a mixture of 1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide prepared as in Ex 1, Step F (200 mg, 0.45 mmol) and TEA (0.5 ml, 3.59 mmol) in DCM (2.5 ml) at –78°C, under N_2(g). The reaction was continued at –78°C for 2 hours and then at room temperature for 19 hours. Water was added and the phases were separated. The organic phase was washed with water and dried over $MgSO_4$. The product was further purified by preparatory HPLC (kromasil C8 column, ammonium

acetate (aq, 0.1 M):acetonitrile, product came at 100% acetonitrile) to give an almost white powder (158 mg, 60%).

^{1}H NMR (399.964 MHz) δ 7.71-7.67 (m, 1H), 7.67-7.57 (br, 1H), 7.50-7.46 (m, 1H), 7.35 (s, 1H), 7.25 (s, 2H), 7.07-7.00 (m, 3H), 6.98-6.92 (m, 2H), 2.86-2.76 (m, 4H), 2.29 (s, 3H), 1.73-1.65 (m, 4H), 1.42-1.33 (m, 2H).

HRMS Calcd for $[C_{26}H_{24}Cl_2N_4O_4S_2+H]^+$: 591.069. Found: 591.067.

Example 13

: 4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl pyridine-3-sulfonate hydrochloride

Step A: 4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl pyridine-3-sulfonate

A suspension of pyridine-3-sulfonyl chloride (144 mg, 0.67 mmol) in DCM (10 ml) was added to a mixture of 1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide, prepared as Ex 1, Step F (200 mg, 0.45 mmol) and TEA (0.5 ml, 3.59 mmol) in DCM (2.5 ml) at –78°C, under N_2(g). The reaction was continued at –78°C for 1.5 hours and then at room temperature for 30 minutes. Water was added and the phases were separated. The organic phase was washed with water and dried over $MgSO_4$. The product was further purified by flash chromatography (SiO_2, toluene:ethyl acetate, product came at 42% ethyl acetate) to give an almost white powder (216 mg, 82%).

^{1}H NMR (399.964 MHz) δ 8.95-8.85 (m, 2H), 8.10-8.04 (m, 1H), 7.64 (s, 1H), 7.50-7.45 (m, 1H), 7.44-7.40 (m, 1H), 7.34-7.24 (m, 2H), 7.09-7.04 (m, 2H), 7.00-6.95 (m, 2H), 2.88-2.78 (m, 4H), 2.33 (s, 3H), 1.78-1.68 (m, 4H), 1.46-1.36 (m, 2H).

HRMS Calcd for $[C_{27}H_{25}Cl_2N_5O_4S+H]^+$: 586.108. Found: 586.111.

Step B: 4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl pyridine-3-sulfonate hydrochloride

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl pyridine-3-sulfonate (150 mg, 0.26 mmol) was dissolved in 0.1 M HCl in acetic acid (10 ml) and freeze dried to give the salt as a white powder (159 mg, 99.8%).

Example 14

tert-butyl [2-(4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenoxy)ethyl]ethylcarbamate

Step A: *tert*-butyl ethyl(2-hydroxyethyl)carbamate

Di-tert-butyl dicarbonate (3.19 g, 14.6 mmol) in THF (10 ml) was added to 2-(ethylamino)ethanol (1.00 g, 11.2 mmol) and reacted at room temperature for 3 hours. The solvent was evaporated at reduced pressure to give the crude product (2.28 g).

^{1}H NMR (499.961 MHz) δ 3.71-3.65 (br, 2H), 3.55-3.35 (br, 1H), 3.35-3.30 (br, 2H), 3.30-3.20 (br, 2H), 1.43 (s, 9H), 1.07 (t, 3H).

Step B: *tert*-butyl [2-(4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenoxy)ethyl]ethylcarbamate

1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide, prepared as Ex 1, Step F (151.6 mg, 0.34 mmol) and *tert*-butyl ethyl(2-hydroxyethyl)carbamate (408.6 mg, 1.73 mmol) were mixed in toluene (1ml) and reacted repeatedly in a single node microwave oven at 180°C. The total reaction time was 2 hours. Cyanomethylenetri-*N*-butylphosphorane was added before each heating (total amount 925 mg, 3.83 mmol). The solvent was then evaporated and the product purified by preparatory HPLC (kromasil C8 column, ammonium acetate (aq, 0.1 M):acetonitrile, product came at 100% acetonitrile) and flash chromatography (SiO_2, toluene:ethylacetate, product came at 30% ethyl acetate) to give an almost white powder (125 mg, 60%).

^{1}H NMR (399.964 MHz) δ 7.62 (s, 1H). 7.37 (s, 1H), 7.23 (s, 2H), 7.01-6.95 (m, 2H), 6.81-6.75 (m, 2H), 4.05-3.95 (br, 2H), 3.55-3.45 (br, 2H), 3.35-3.25 (br, 2H), 2.86-2.78 (br, 4H), 2.32 (s, 3H), 1.75-1.65 (m, 4H), 1.41 (s, 9H), 1.45-1.35 (m, 2H), 1.08 (t, 3H).

MS *m/z* 616, 618, 620 $(M+H)^+$.

Example 15

1-(2,4-dichlorophenyl)-5-{4-[2-(ethylamino)ethoxy]phenyl}-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide dihydrochloride

Thionyl chloride (1 ml, 13.71 mmol) in methanol (10 ml) was added to a suspension of *tert*-butyl [2-(4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenoxy)ethyl]ethylcarbamate from Ex 14, Step B (137 mg, 0.22 mmol) in methanol (2 ml). After 2.5 hours the solvent was evaporated and the product freeze dried. The compound was purified by preparatory HPLC (kromasil C8 column, ammonium acetate (aq, 0.1 M):acetonitrile, product came at 72% acetonitrile), freeze dried and finally dissolved in 0.1 M HCl in acetic acid (15 ml) and freeze dried again to give an almost white powder (53 mg, 40%).

^{1}H NMR (399.964 MHz) δ 7.54-7.47 (m, 2H), 7.44-7.39 (m, 1H), 7.19-7.14 (m, 2H), 7.01-6.96 (m, 2H), 4.24 (t, 2H), 3.41 (t, 2H), 3.18-3.06 (m, 6H), 2.27 (s, 3H), 1.87-1.78 (m, 4H), 1.57-1.48 (m, 2H), 1.32 (t, 3H).

HRMS Calcd for $[C_{26}H_{31}Cl_2N_5O_2+H]^+$: 516.193. Found: 516.195.

Example 16

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl 3-methylbutane-1-sulfonate

3-Methylbutane-1-sulfonyl chloride (84 mg, 0.49 mmol) in DCM (2 ml) was added to a mixture of 1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide, prepared as in Example 1, Step F (100 mg, 0.23 mmol) and TEA (0.5 ml, 3.59 mmol) in DCM (2 ml) at –78°C, under N_2(g). The reaction was continued at –78°C for 1 hour. Water was added and the phases were separated. The organic phase was washed with water and dried over $MgSO_4$. The product was further purified by preparatory HPLC (kromasil C8 column, ammonium acetate (aq, 0.1 M):acetonitrile, product came at 100% acetonitrile) to give an almost white powder (94 mg, 72%).

^{1}H NMR (399.964 MHz) δ 7.85-7.45 (br, 1H), 7.38 (s, 1H), 7.29-7.25 (m, 2H), 7.23-7.18 (m, 2H), 7.16-7.11 (m, 2H), 3.25-3.18 (m, 2H), 2.88-2.80 (m, 4H), 2.33 (s, 3H), 1.86-1.77 (m, 2H), 1.76-1.65 (m, 5H), 1.45-1.34 (m, 2H), 0.92 (d, 6H).

HRMS Calcd for $[C_{27}H_{32}Cl_2N_4O_4S+H]^+$: 579.160. Found: 579.159.

Example 17

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl 3,3-dimethylbutane-1-sulfonate

3,3-Dimethylbutane-1-sulfonyl chloride (59 mg, 0.32 mmol) in DCM (2 ml) was added to a mixture of 1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide, prepared as in Example 1, Step F (103 mg, 0.23 mmol) and TEA (0.5 ml, 3.59 mmol) in DCM (2 ml) at –78°C, under N_2(g). The reaction was continued at –78°C for 1 hour. Water was added and the phases were separated. The organic phase was washed with water and dried over $MgSO_4$. The product was further purified by preparatory HPLC (kromasil C8 column, ammonium acetate (aq, 0.1 M):acetonitrile, product came at 100% acetonitrile) to give an almost white powder (94 mg, 68%).

^{1}H NMR (399.964 MHz) δ 8.20-7.40 (br, 1H), 7.36 (s, 1H), 7.28-7.22 (m, 2H), 7.21-7.16 (m, 2H), 7.15-7.09 (m, 2H), 3.20-3.13 (m, 2H), 2.87-2.80 (m, 4H), 2.31 (s, 3H), 1.83-1.76 (m, 2H), 1.73-1.65 (m, 4H), 1.43-1.32 (m, 2H), 0.89 (s, 9H).

HRMS Calcd for $[C_{28}H_{34}Cl_2N_4O_4S+H]^+$: 593.176. Found: 593.176.

Example 18

4-[1-(2,4-dichlorophenyl)-4-methyl-3-({[5-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)-1*H*-pyrazol-5-yl]phenyl 3,3,3-trifluoropropane-1-sulfonate

Step A: 5-[4-(benzyloxy)phenyl]-1-(2,4-dichlorophenyl)-4-methyl-*N*-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrazole-3-carboxamide

Oxalyl chloride (1 ml) in DCM (4 ml) was added to a suspension of 5-[4-(benzyloxy)phenyl]-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid, prepared as in Example 1, Step D (202 mg, 0.45 mmol) in DCM (4 ml). 1 drop of DMF was added and the reaction continued at room temperature for 1 hour. DCM and excess oxalyl chloride were removed at reduced pressure and the acid chloride suspended in DCM (4 ml) and added to 5-(trifluoromethyl)pyridine-2-amine (87.6 mg, 0.54 mmol) in DCM/K_2CO_3 (10%, aq) (1/1, 8 ml). The reaction was continued at room temperature for 24 hours. Then 50 mg DMAP was added and the reaction continued at room temperatue for 1 hour. The phases were separated and the organic phase washed with water and dried over $MgSO_4$. The product was purified further by flash chromatography (SiO_2, toluene) (108 mg, 41%).

^{1}H NMR (399.964 MHz) δ 9.66 (s, 1H), 8.58-8.48 (m, 2H), 7.95-7.90 (m, 1H), 7.44-7.14 (m, 8H), 7.10-7.04 (m, 2H), 6.94-6.90 (m, 2H), 5.02 (s, 2H), 2.42 (s, 3H).

MS *m/z* 597, 599, 601 $(M+H)^+$.

Step B: 1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-*N*-[5-(trifluoromethyl)pyridine-2-yl]-1*H*-pyrazole-3-carboxamide

5-[4-(benzyloxy)phenyl]-1-(2,4-dichlorophenyl)-4-methyl-*N*-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrazole-3-carboxamide (108 mg, 0.18 mmol) was suspended in 4.1 M HBr in acetic acid (10 ml) and reacted at room temperature for 6 hours. Ethanol was added (95%, 75 ml) and the solvent evaporated at reduced pressure. Methanol was added and the product was neutralised with $NaHCO_3$ (1M, aq). The solvent was evaporated and the mixture dissolved in DCM and water. The phases were separated and the organic phase washed with water and dried over $MgSO_4$ (87 mg, 95%).

^{1}H NMR (399.964 MHz) δ 9.64 (s, 1H), 8.58-8.48 (m, 2H), 7.97-7.91 (m, 1H), 7.45-7.41 (m, 1H), 7.32-7.23 (m, 2H), 7.03-6.98 (m, 2H), 6.80-6.75 (m, 2H), 5.50-5.30 (br, 1H), 2.40 (s, 3H).

MS *m/z* 507, 509, 511 $(M+H)^+$.

Step C: 4-[1-(2,4-dichlorophenyl)-4-methyl-3-({[5-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)-1*H*-pyrazol-5-yl]phenyl 3,3,3-trifluoropropane-1-sulfonate

3,3,3-trifluoropropane-1-sulfonyl chloride (105 mg, 0.53 mmol) was added to a mixture of 1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-*N*-[5-(trifluoromethyl)pyridine-2-yl]-1*H*-pyrazole-3-carboxamide (87 mg, 0.17 mmol) and TEA (0.5 ml, 3.59 mmol) in DCM (3 ml) at –78°C, under N_2(g). The reaction was continued at –78°C for 2 hours and then at room temperature over night. Water was added and the phases were separated. The organic phase was washed with water and dried over $MgSO_4$. The product was further purified by preparatory HPLC (kromasil C8 column, ammonium acetate (aq, 0.1 M):acetonitrile, product came at 100% acetonitrile) to give an almost white powder (86 mg, 75%).

^{1}H NMR (399.964 MHz) δ 9.70 (s, 1H), 8.57-8.48 (m, 2H), 7.99-7.92 (m, 1H), 7.43 (s, 1H), 7.32 (s, 2H), 7.28-7.19 (m, 4H), 3.53-3.44 (m, 2H), 2.85-2.71 (m, 2H), 2.42 (s, 3H).

HRMS Calcd for $[C_{26}H_{18}Cl_2F_6N_4O_4S+H]^+$: 667.041. Found: 667.031.

Example 19

1-(2,4-dichlorophenyl)-5-{4-[2-(1,3-dioxolan-2-yl)ethoxy]phenyl}-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide

2-(2-bromoethyl)-1,3-dioxolane (60 mg, 0.33 mmol), 1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide prepared as in Ex.1, Step F (100 mg, 0.22 mmol) and potassium carbonate (150 mg, 1.09 mmol) were refluxed in acetonitrile (25 ml) for 15 hours. The solvent was evaporated, water and DCM were added, the phases separated and the organic phase washed with water and dried ($MgSO_4$). The product was further purified by preparatory HPLC (kromasil C8 column, ammonium acetate (aq, 0.1 M):acetonitrile, product came at 100% acetonitrile) to give an almost white powder (60 mg, 49%).

^{1}H NMR (399.964 MHz) δ 7.80-7.50 (br, 1H), 7.36 (s, 1H), 7.21 (s, 2H), 7.00-6.94 (m, 2H), 6.80-6.74 (m, 2H), 5.02 (t, 1H), 4.04 (t, 2H), 3.96-3.78 (m, 4H), 2.86-2.78 (m, 4H), 2.30 (s, 3H), 2.09 (q, 2H), 1.74-1.65 (m, 4H), 1.42-1.32 (m, 2H).

HRMS Calcd for $[C_{27}H_{30}Cl_2N_4O_4+H]^+$: 545.172. Found: 545.172.

Example 20

Propane-1-sulfonic acid 4-[2-(2,4-dichloro-3-fluorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester

Step A: 1-(2,4-Dichloro-3-fluorophenyl)-5-(4-methoxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid

A solution of sodium ethoxide was generated from sodium metal (0.18 g, 7.89 mmol) in 20 ml abs. ethanol. To this solution was added 2-acetyl-4-(4-methoxy-phenyl)-3-methyl-4-oxo-butyric acid ethyl ester (1.73 g, 5.92 mmol) and the reaction mixture stirred at room temperature for 30 min. A previously prepared solution of 2,4-dichloro-3-fluorodiazonium chloride (prepared from 2,4-dichloro-3-fluoroaniline (1.30 g, 7.22 mmol) in 3 ml 24% HCl and sodium nitrite (0.51 g, 7.39 mmol) in 3.5 ml water at 0 °C) was added in 5 portions keeping the temperature below 5 °C. After stirring at room temperature for 2.5 hours water was added, the product extracted with EtOAc (3 x). The combined organic extracts was dried (Na_2SO_4), filtered and evaporated. The residue was dissolved in ethanol (40 ml) and sodium hydroxide (1.00 g, 25.0 mmol) in 5 ml of water was added. After 2 hours boiling under reflux the reaction mixture was cooled, acidified with HCl and the product extracted with EtOAc (3 x). After washing, drying (Na_2SO_4), filtration and concentration, the residue was purified by flash chromtography (hexane : EtOAc 70:30 – 50:50) affording 1.37 g (31%) of the title compound as a light brown solid.

Step B: 1-(2,4-Dichloro-3-fluoro-phenyl)-5-(4-methoxy-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide

1-(2,4-Dichloro-3-fluoro-phenyl)-5-(4-methoxy-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid (1.37 g, 3.43 mmol) was suspended in dichloromethane (20 ml) and a few drops of DMF added followed by the addition of oxalylchloride (0.87 g, 6.86 mmol). The reaction mixture was refluxed for two hours. After cooling to room temperature the solvent was removed and the crude acid chloride redissolved in dichloromethane (20 ml), cooled to 0 °C, Et_3N (0.96 ml, 6.94 mmol) was added followed by 1-aminopiperidine (0.37 ml, 3.62 mmol). The cooling bath was removed and the reaction mixture stirred at room temperature overnight. Water was added and the product extracted with dichloromethane (3x), the combined extracts dried (Na_2SO_4), filtered and evaporated. Flash chromatography

(hexane : EtOAc 50 : 50) afforded 0.79 g (48%) of the title compound as a light brown solid.

Step C: 1-(2,4-Dichloro-3-fluoro-phenyl)-5-(4-hydroxy-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide

1-(2,4-Dichloro-3-fluoro-phenyl)-5-(4-methoxy-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide (0.79 g, 1.66 mmol) was dissolved in 40 ml of dichloromethane at 0 °C. Boron tribromide (0.32 ml, 3.31 mmol) was added, the cooling bath was removed and stirring continued for 2 hrs at room temperature before pouring it onto ice-water and extracting with DCM (x3). The combined extracts were dried (Na_2SO_4), filtered and concentrated. Flash chromatography (EtOAc) afforded 0.36 g (47%) of the title compound as a colorless solid.

Step D: Propane-1-sulfonic acid 4-[2-(2,4-dichloro-3-fluoro-phenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]-phenyl ester

To a solution of 1-(2,4-dichloro-3-fluoro-phenyl)-5-(4-hydroxy-phenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide (0.36 g, 0.78 mmol) in dichloromethane (10 ml) was added triethylamine (0.22 ml, 1.56 mmol) and the reaction mixture cooled to 0 °C. 1-Propanesulfonylchloride (0.22 g, 1.56 mmol) was added, the cooling bath removed and the reaction mixture stirred at rt for 2 hrs. Water was added, the product extracted with DCM (x2), the combined organic extracts washed with water, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (hexane : EtOAc gradient) afforded 100 mg (23%) of the title compound as a colorless solid. HPLC 80% purity. Preparative HPLC afforded 40 mg of the title compound.

^{1}H NMR ($CDCl_3$): δ 7.50-7.20 (7 H, m), 3.57-3.23 (6H, m), 2.37 (3H, s),2.10-1.80 (6H, m), 1.70-1.50 (2H, m), 1.10 (3H, t)

MS: 591 (M+Na)

HPLC: 97.1%

Example 21

5-Chlorothiophene-2-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester

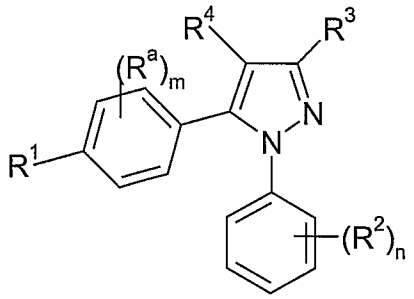
1-(2,4-Dichloro-phenyl)-5-(4-hydroxy-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide, prepared as in Ex 1, Step F (100 mg, 0.22 mmol) was dissolved in dry dichloromethane (3 ml) under nitrogen atmosphere and triethyl amine (0.09 ml) was added.

5-Chlorothiophene-2-sulfonyl chloride (0.54 mg, 0.24 mmol), dissolved in dry dichloromethane (2 ml), was then added. The reaction mixture was stirred over the weekend at room temperature. The reaction mixture was diluted with dichloromethane to 20 ml and was then washed with water (2x5 ml) and brine (5 ml). The organic layer was concentrated under reduced pressure to give an oil. The crude material was purified by reverse phase HPLC, Kromasil C8, 5-100% MeCN in water with 0.1M ammonium acetate. The product fraction was concentrated under reduced pressure and the residue was dissolved in dichloromethane and washed with water and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the title compound as a yellow solid.

^{1}H-NMR ($CDCl_3$): δ 1.42-1.50 (m, 2H), 1.73-1.81 (m, 4H), 2.39 (s, 3H), 2.84-2.92 (m, 4H), 6.95 (d, 1H), 7.04-7.14 (m, 4H), 7.30-7.36 (m, 3H), 7.44 (d, 1H), 7.63 (s, 1H).
MS: 625 (M+1). HPLC: >99% purity.

Claims

1. A compound of formula (I)



I

and pharmaceutically acceptable salts thereof, in which

R^1 represents a) a C_{1-3}alkoxy group substituted by one or more of the following i) fluoro ii) a group NR^cR^d in which R^c and R^d independently represent H, a C_{1-6}alkyl group or C_{1-6}alkoxycarbonyl group provided that one of R^c and R^d is other than H or iii) a 1,3-dioxolan-2-yl group b) R^1 represents a C_{4-6}alkoxy group optionally substituted by one or more of the following i) fluoro ii) a group NR^cR^d in which R^c and R^d independently represent H, a C_{1-6}alkyl group or C_{1-6}alkoxycarbonyl group provided that one of R^c and R^d is other than H or iii) a 1,3-dioxolan-2-yl group c) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, d) a group $R^5S(O)_2O$ or $R^5S(O)_2NH$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, or R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z e) a group of formula $(R^6)_3$ Si in which R^6 represents a C_{1-6}alkyl group which may be the same or different or f) a group of formula $R^bO(CO)O$ in which R^b represents a C_{1-6}alkyl group optionally substituted by one or more fluoro;

R^a represents halo, a C_{1-3}alkyl group or a C_{1-3}alkoxy group;

m is 0, 1, 2 or 3;

R^2 represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, nitro, cyano or halo

n is 0, 1, 2 or 3;

R^3 represents

a) a group X-Y-NR^7R^8

in which X is CO or SO_2,

Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group;

and R^7 and R^8 independently represent :

a C_{1-6}alkyl group optionally substituted by 1, 2, or 3 groups represented by W;

a C_{3-15}cycloalkyl group optionally substituted by 1, 2, or 3 groups represented by W;

a (C_{3-15}cycloalkyl)C_{1-3}alkylene group optionally substituted by 1, 2, or 3 groups represented by W;

a group $-(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group, a C_{1-5}alkoxy group or halo wherein the alkyl and alkoxy group are optionally independently substituted by one of more fluoro;

or R^7 represents H and R^8 is as defined above;

or R^7 and R^8 together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy, fluoro or benzyl;

or b) oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thienyl, furyl or oxazolinyl,

each optionally substituted by 1, 2 or 3 groups Z;

R^4 represents H, halo, hydroxy, cyano, a C_{1-6}alkyl group, a C_{1-6}alkoxy group or a C_{1-6}alkoxyC_{1-6}alkylene group which contains a maximum of 6 carbon atoms, each of which groups is optionally substituted by one or more fluoro or cyano;

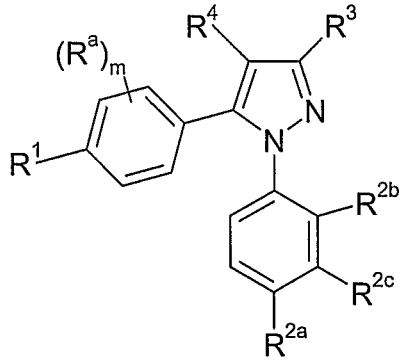
Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C_{1-3}alkylamino, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl and acetyl; and

W represents hydroxy, fluoro, a C_{1-3}alkyl group, a C_{1-3}alkoxy group, amino, mono or di C_{1-3}alkylamino, a C_{1-6}alkoxycarbonyl group or a heterocyclic amine selected from morpholinyl, pyrrolidinyl, piperdinyl or piperazinyl in which the heterocyclic amine is optionally substituted by a C_{1-3}alkyl group or hydroxyl;

but excluding 1,1-dimethylethyl [2-[4-[3-[(ethylmethylamino)carbonyl]-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy]ethyl]carbamate and 1,1-dimethylethyl [2-[4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1*H*-pyrazol-5-yl]phenoxy]ethyl]carbamate.

2. A compound as claimed in claim 1 in which R^3 represents a group as described in paragraph a) above.

3. A compound as claimed in claim 1 as represented by formula IA



IA

in which R^1 is
a) a C_{4-6}alkoxy group optionally substituted by one or more fluoro, b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^5S(O)_2O$ or $R^5S(O)_2NH$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, or R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z wherein Z is as previously defined d) a group of formula $(R^6)_3$ Si in which R^6 represents a C_{1-6}alkyl group which may be the same or different or e) a group of formula $R^bO(CO)O$ in which R^b represents a C_{1-6}alkyl group optionally substituted by one or more fluoro;

R^a represents halo and m is 0, 1 or 2;

R^{2a} represents chloro;

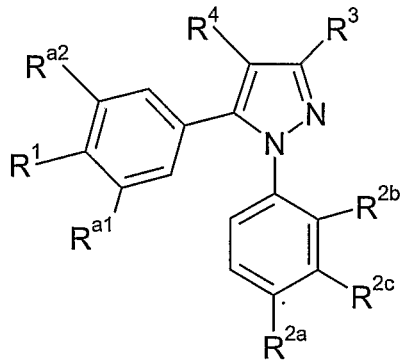
R^{2b} represents chloro;

R^{2c} represents H or fluoro;

R^3 represents a group $CONHNR^7R^8$ in which NR^7R^8 represents piperidino or morpholino or R^3 represents a group $CONHR^8$ in which R^8 represents a C_{5-7}cycloalkyl group optionally substituted by a C_{1-6}alkoxycarbonyl group or R^8 represents an optionally substituted pyridyl; and

R^4 represents H, a C_{1-3}alkyl group or halo.

4. A compound as claimed in claim 1, as represented by formula IB



IB

in which R^1 is
a) a C_{4-6}alkoxy group optionally substituted by one or more fluoro, b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, c) a group $R^5S(O)_2O$ or $R^5S(O)_2NH$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, or R^5 represents phenyl or a heteroaryl group each of which is optionally substituted by 1, 2 or 3 groups represented by Z or d) a group of formula $(R^6)_3$ Si in which R^6 represents a C_{1-6}alkyl group which may be the same or different;

R^{a1} represents halo or H;

R^{a2} represents halo or H;

R^{2a} represents chloro;

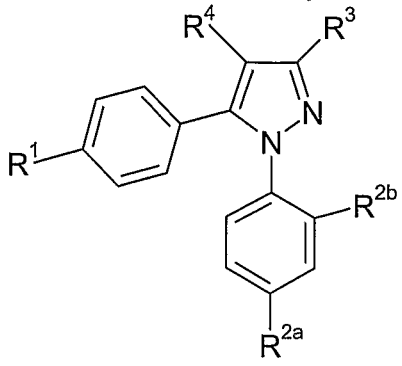
R^{2b} represents chloro;

R^{2c} represents halo or H;

R^3 represents a group $CONHNR^7R^8$ in which NR^7R^8 represents piperidino; and

R^4 represents a C_{1-3}alkyl group.

5. A compound as claimed in claim 1 as represented by formula IC



IC

in which R^1 is

a) a C_{4-6}alkoxy group optionally substituted by one or more fluoro, b) a group $R^5S(O)_2O$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro;

R^{2a} represents chloro;

R^{2b} represents chloro;

R^3 represents a group $CONHNR^7R^8$ in which NR^7R^8 represents piperidino or morpholino; and

R^4 represents a C_{1-3}alkyl group or halo.

6. A compound as claimed in any previous claim in which R^1 is a group $R^5S(O)_2O$ in which R^5 represents a C_{1-6}alkyl group optionally substituted by one or more fluoro.

7. A compound as claimed in any any one of claims 1 to 5 in which R^1 is a C_{4-6}alkoxy group substituted by one or more fluoro.

8. A compound selected from one or more of the following:

butane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

1-(2,4-dichlorophenyl)-4-methyl-5-[4-(4,4,4-trifluorobutoxy)phenyl]-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide;

propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)2*H*-pyrazol-3-yl]phenyl ester;

propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(morpholin-4-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

3,3,3-trifluoropropane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

4,4,4-trifluorobutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

propane-1-sulfonic acid-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]-2,6-difluorophenyl ester;

propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

propane-1-sulfonic acid 4-[4-bromo-2-(2,4-dichlorophenyl)-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

methyl 1-{[(1-(2,4-dichlorophenyl)-4-methyl-5-{4[(propylsulfonyl)oxy]phenyl}-1*H*-pyrazol-3-yl)carbonyl]amino}cyclopentanecarboxylate;

carbonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidine-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]-phenyl ester propyl ester;

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl thiophene-2-sulfonate;

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl pyridine-3-sulfonate;

tert-butyl [2-(4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenoxy)ethyl]ethylcarbamate;

1-(2,4-dichlorophenyl)-5-{4-[2-(ethylamino)ethoxy]phenyl}-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide;

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl 3-methylbutane-1-sulfonate;

4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl 3,3-dimethylbutane-1-sulfonate;

4-[1-(2,4-dichlorophenyl)-4-methyl-3-({[5-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)-1*H*-pyrazol-5-yl]phenyl 3,3,3-trifluoropropane-1-sulfonate;

1-(2,4-dichlorophenyl)-5-{4-[2-(1,3-dioxolan-2-yl)ethoxy]phenyl}-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide;

propane-1-sulfonic acid 4-[2-(2,4-dichloro-3-fluorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2*H*-pyrazol-3-yl]phenyl ester;

5-chloro-thiophene-2-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester;

as well as pharmaceutically acceptable salts thereof.

9. A compound of formula I as claimed in any one of claims 1 to 8 for use as a medicament.

10. A pharmaceutical formulation comprising a compound of formula I as claimed in any one of claims 1 to 8 and a pharmaceutically acceptable adjuvant, diluent or carrier.

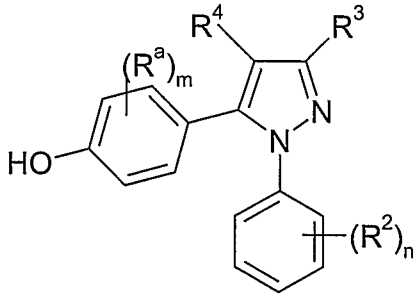
11. Use of a compound of formula I as claimed in as claimed in any one of claims 1 to 8 in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy and related conditions, and neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications.

12. A method of treating obesity, psychiatric disorders, psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy and related conditions, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal system, and

extended abuse, addiction and/or relapse indications, comprising administering a pharmacologically effective amount of a compound of formula I as claimed in as claimed in any one of claims 1 to 8 to a patient in need thereof.

13. A compound as defined in as claimed in any one of claims 1 to 8 for use in the treatment of obesity.

14. A process for the preparation of compounds of formula I in which R^1 represents a) a C_{1-3}alkoxy group substituted by one or more fluoro or C_{4-6}alkoxy group optionally substituted by one or more fluoro or b) a group of formula phenyl$(CH_2)_pO$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, or c) a group $R^5S(O)_2O$ comprising reacting a compound of formula III



III

in which R^a, R^2, R^3, R^4, m and n are as previously defined with either

a) an alkylating agent of formula R^9X in which R^9 represents a C_{1-3}alkyl group substituted by one or more fluoro or C_{4-6}alkyl group optionally substituted by one or more fluoro and X represents a leaving group in an inert solvent in the presence of a base at a temperature in the range of -25°C to 150°C; or

b) an alkylating agent of formula R^9X in which R^9 represents a group of formula phenyl$(CH_2)_p$- in which p is 1, 2 or 3 and the phenyl ring is optionally substituted by 1, 2 or 3 groups represented by Z, and X represents a leaving group in an inert solvent in the presence of a base at a temperature in the range of -25°C to 150°C; or

c) a sulphonating agent of formula R^5SO_2L in which R^5 is as previously defined and L represents a leaving group in an inert solvent in the presence of a base at a temperature in the range of -25°C to 150°C; respectively.