PYRAZOLE DERIVATIVES AS THERAPEUTIC AGENTS

Field of the invention

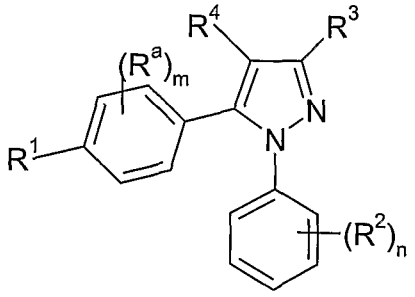
The present invention relates to certain salts of 1,5-diarylpyrazole-3-carboxamides, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.

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.

Co-pending PCT application No. PCT/GB2005/000534 discloses compounds of formula A



A

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.

Salts are mentioned in general terms in PCT/GB2005/000534 in the following way: "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 A is, for example, an acid-addition salt of a compound of Formula A 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 A 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.

Only 2 specific salts of compounds of Formula A are disclosed in PCT/GB2005/000534. These are: 4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl pyridine-3-sulfonate hydrochloride and 1-(2,4-dichlorophenyl)-5-{4-[2-(ethylamino)ethoxy]phenyl}-4-methyl-*N*-piperidin-1-yl-1*H*-pyrazole-3-carboxamide dihydrochloride both of which are excluded from the claims of the present invention.

Further salts with suitable properties for pharmaceutical formulation have now been found.

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations comprising the active compound.

Further, in the manufacture of drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of drug is provided following administration to a patient.

Chemical stability, solid-state stability, and "shelf life" of the active ingredients are also very important factors. The drug substance, and compositions containing it, should preferably be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physico-chemical characteristics (e.g. its chemical composition, density, hygroscopicity and solubility).

Moreover, it is also important to be able to provide the drug in a form that is as chemically pure as possible.

The skilled person will appreciate that, typically, if a drug can be readily obtained in a stable form, such as a stable crystalline form, advantages may be provided, in terms of ease of handling, ease of preparation of suitable pharmaceutical formulations, and a more reliable solubility profile.

Description of the invention

The present invention provides a compound selected from:

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;

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;

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

in the form of a methanesulphonate salt (mesylates salt) , a hemi-1,5-naphthalenedisulphonate salt, a 1,2-ethanedisulfonic acid salt, a hydrochloride salt or a hydrogen sulphate salt but excluding 4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl pyridine-3-sulfonate hydrochloride.

In a particular aspect the present invention provides one or more of the following:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3-methylbutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hemi-1,5-naphthalenedisulphonate;
3,3-dimethylbutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hydrochloride;
3,3-dimethylbutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester mesylate;
3,3-dimethylbutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hemi-1,5-naphthalenedisulphonate;
propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hydrochloride;
propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester mesylate;
propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hemi-1,5-naphthalenedisulphonate;
propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hydrogen sulphate;
carbonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester propyl ester hydrochloride;
carbonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester propyl ester mesylate;
carbonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester propyl ester hemi-1,5-naphthalenedisulphonate;
pyridine-3-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester mesylate;
pyridine-3-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hemi-1,5-naphthalenedisulphonate.

It will be understood that the present invention includes one or any combination of more than one of the above salts.

We have found that certain compounds of the invention have the advantage that they may be prepared in crystalline form.

According to a further aspect of the invention there is provided a compound of the invention in substantially crystalline form.

Although we have found that it is possible to produce compounds of the invention in forms which are greater than 80% crystalline, by "substantially crystalline" we include greater than 20%, preferably greater than 30%, and more preferably greater than 40% (e.g. greater than any of 50, 60, 70, 80 or 90%) crystalline.

According to a further aspect of the invention there is also provided a compound of the invention in partially crystalline form. By "partially crystalline" we include 5% or between 5% and 20% crystalline.

The degree (%) of crystallinity may be determined by the skilled person using X-ray powder diffraction (XRPD). Other techniques, such as solid state NMR, FT-IR, Raman spectroscopy, differential scanning calorimetry (DSC) and microcalorimetry, may also be used.

Compounds of the invention, and particularly crystalline compounds of the invention, may have improved stability when compared to compounds disclosed in PCT/GB2005/000534.

The term "stability" as defined herein includes chemical stability and solid state stability.

By "chemical stability", we include that it may be possible to store compounds of the invention in an isolated form, or in the form of a formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of chemical degradation or decomposition.

By "solid state stability", we include that it may be possible to store compounds of the invention in an isolated solid form, or in the form of a solid formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of solid state transformation (e.g. crystallisation, recrystallisation, solid state phase transition, hydration, dehydration, solvatisation or desolvatisation).

Examples of "normal storage conditions" include temperatures of between minus 80 and plus 50°C (preferably between 0 and 40°C and more preferably room temperatures, such as 15 to 30°C), pressures of between 0.1 and 2 bars (preferably at atmospheric pressure), relative humidities of between 5 and 95% (preferably 10 to 60%), and/or

exposure to 460 lux of UV/visible light, for prolonged periods (i.e. greater than or equal to six months). Under such conditions, compounds of the invention may be found to be less than 15%, more preferably less than 10%, and especially less than 5%, chemically degraded/decomposed, or solid state transformed, as appropriate. The skilled person will appreciate that the above-mentioned upper and lower limits for temperature, pressure and relative humidity represent extremes of normal storage conditions, and that certain combinations of these extremes will not be experienced during normal storage (e.g. a temperature of 50°C and a pressure of 0.1 bar).

It may be possible to crystallise salts of compounds of the present invention with or without the presence of a solvent system (e.g. crystallisation may be from a melt, under supercritical conditions, or achieved by sublimation). However, it is preferable that crystallisation occurs from an appropriate solvent system.

According to a further aspect of the invention, there is provided a process for the preparation of a crystalline compound of the invention which comprises crystallising a compound of the invention from an appropriate solvent system.

Crystallisation temperatures and crystallisation times depend upon the salt that is to be crystallised, the concentration of that salt in solution, and the solvent system that is used.

Crystallisation may also be initiated and/or effected by way of standard techniques, for example with or without seeding with crystals of the appropriate crystalline compound of the invention.

Different crystalline forms of the compounds of the invention may be readily characterised using X-ray powder diffraction (XRPD) methods, for example as described hereinafter.

In order to ensure that a particular crystalline form is prepared in the absence of other crystalline forms, crystallisations are preferably carried out by seeding with nuclei and/or seed crystals of the desired crystalline form in substantially complete absence of nuclei and/or seed crystals of other crystalline forms. Seed crystals of appropriate compound may be prepared, for example, by way of slow evaporation of solvent from a portion of solution of appropriate salt.

Compounds of the invention may be isolated using techniques which are well known to those skilled in the art, for example decanting, filtering or centrifuging.

Compounds may be dried using standard techniques.

Further purification of compounds of the invention may be effected using techniques, which are well known to those skilled in the art. For example impurities may be removed by way of recrystallisation from an appropriate solvent system. Suitable temperatures and times for the recrystallisation depend upon the concentration of the salt in solution, and upon the solvent system that is used.

When compounds of the invention are crystallised, or recrystallised, as described herein, the resultant salt may be in a form which has improved chemical and/or solid state stability, as mentioned hereinbefore.

Compounds of the invention have the advantage that they may be more efficacious, be less toxic, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, be more easily absorbed, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance), than, and/or have other useful pharmacological, physical, or chemical, properties over, compounds known in the prior art. Compounds of the invention may have the further advantage that they may be administered less frequently than compounds known in the prior art.

Compounds of the invention may also have the advantage that they are in a form which provides for improved ease of handling. Further, compounds of the invention have the advantage that they may be produced in forms which may have improved chemical and/or solid state stability (including e.g. due to lower hygroscopicity). Thus, such compounds of the invention may be stable when stored over prolonged periods.

Compounds of the invention may also have the advantage that they may be crystallised in good yields, in a high purity, rapidly, conveniently, and at a low cost.

It will also be understood that the compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated and unsolvated forms.

Methods of preparation

The compounds of the invention may be prepared as outlined below. However, the invention is not limited to these methods.

The salts may be prepared by reacting a compound prepared as described in PCT/GB2005/000534 and in the examples section of this application with the appropriate acid, for example methanesulphonic acid, naphthalene-1,5-disulphonic acid, 1,2-

ethanedisulfonic acid, sulphuric acid or hydrochloric acid in an inert solvent, for example butanone at a temperature in the range of 0-100°C and isolating the solid salt. The salt may be isolated by cooling the reaction solution and optionally seeding the solution with the desired product and/or concentrating the solution. Optionally the product may be isolated by adding an antisolvent to a solution of the product in an inert solvent. The solid may be collected by methods known to those skilled in the art for example filtration or centrifugation.

Particularly a molar equivalent of acid with respect to the free base is used for methanesulphonic acid and hydrochloric acid whereas for sulphuric acid, 1,5-naphthalenedisulphonic and 1,2- ethanedisulfonic acid a half a molar equivalent is used with respect to the free base. It will be appreciated that a slight excess of either the basic compound or the acid may be employed. For example with sulphuric acid a ratio of 1 molar equivalents to 0.5 molar equivalents of base may be employed.

The expression "inert solvent" refers to a liquid that dissolves or partially dissolves the free base and/or the acid and/or the product salt but does not react with the starting materials, reagents, intermediates or products in a manner that adversely affects the yield of the desired product.

In another aspect the present invention provides the compound obtainable by reacting one of the following:

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

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

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

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

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

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

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

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

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

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

with either

a) a molar equivalent hydrochloric acid or

b) a molar equivalent methanesulphonic acid or

c) a half a molar equivalent of sulphuric acid or

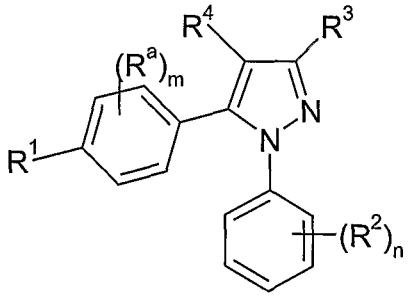
d) a half a molar equivalent of 1,5-naphthalenedisulphonic acid or

e) a half a molar equivalent of 1,2-ethanedisulfonic acid

in butanone.

It will be understood by those skilled in the art that the molar equivalents used are within the range of experimental error and may include a slight excess of one of the reactants for example plus or minus 10% of the theoretical equivalent weight.

In another aspect the present invention provides a compound of formula I



I

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 the form of a methanesulphonate salt, a hemi-1,5-naphthalenedisulphonate salt, or a 1,2-ethanedisulfonic acid salt.

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 rhythms, and arrhythmias, 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 the invention as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of the invention 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 the invention 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 the invention 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 the invention in the preparation of a medicament for the treatment or prophylaxis of immune, cardiovascular disorders (e.g. atherosclerosis, arteriosclerosis, angina pectoris, abnormal heart rhythms, and arrhythmias, 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 the invention 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 the invention 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 the invention 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 the invention 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 the invention to a patient in need thereof for the prophylaxis or treatment of immune, cardiovascular disorders (e.g. atherosclerosis, arteriosclerosis, angina pectoris, abnormal heart rhythms, and arrhythmias, 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 the invention 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 the invention as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of the invention 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 the invention 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.

The compounds of the present invention are suitable for use in treating the above indications in juvenile or adolescent patient populations.

The compounds of the present invention may also be suitable for use in the regulation of bone mass and bone loss and therefore useful in the treatment of osteoporosis and other bone diseases.

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 the invention, 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 invention, 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 invention, 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 the invention, 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 the invention, 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 the invention, 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 the invention, 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 the invention, 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 the invention, 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 invention, 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 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 invention, 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 invention, 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.

The compounds of the invention are 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 of the Invention

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
LiHMDSA	Lithium bis(trimethylsilyl)amide bis(trimethylsilyl)amide
MEK	Methyl ethyl ketone
MeOH	methanol
MeCN	acetnitrile
NMM	4-methylmorpholine
NMP	N-methylpyrrolidone
rt or RT	room temperature
TBTU	O-(Benzotriazole-1-yl)-N,N,N', N'-tertamethyluronium
TEA	triethylamine
TFA	Trifluoroacetic acid
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). ^{1}H NMR measurements were performed on either a Varian Mercury 300 or a Varian Inova 500, operating at ^{1}H 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

General procedure for salt preparation

The free base (usually 15-30 mg) was dissolved in butanone (for example 0.08 to 0.2 ml usually 0.8-2 ml) and if necessary together with methanol (usually less than 1 ml). The solution was optionally put in an ultrasonic bath (Decon FS200b). Acid (1 molar equivalent (equiv.) HCl or 1 equiv. methanesulphonic acid or 0.5 equiv. naphthalene-1,5-disulphonic acid) or 1 equiv. or 0.5 equiv. sulphuric acid, dissolved in methanol (usually 0.1-0.2 ml), was added. Heptane (usually 0.5-2 ml) was added dropwise and the resulting mixture was left in the ultrasonic bath. The formed solid was collected by filtration and was dried under high vacuum.

The melting points were determined on a Reichert melting point microscope and are uncorrected. It will be appreciated by those skilled in the art that the rate of heating can affect the melting point obtained and that certain salts, for example hydrochloride salts, may dissociate on slow heating so that ultimately the melting point obtained may be that of the free base or that of a mixture of free base and hydrochloride salt. In such cases combustion analysis may be used to confirm the identity of the salt. It will also be appreciated by those skilled in the art that the drying temperature should not be too high, for example greater than 45^0C, otherwise decomposition of the salt may occur. Vacuum drying is preferred.

The following salts were formed as described in the general procedure by using appropriate acid.

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

Hydrochloride: melting point 106-112°C.

Hemi-1,5-naphthalenedisulphonate: melting point 160-163 °C.

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

Hydrochloride: melting point 220-223 °C.

Hemi-1,5-naphthalenedisulphonate: melting point 270-274 °C.

Mesylate: melting point 218-223 °C.

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

Hydrochloride: melting point: 100-105 °C

Mesylate: melting point 169-174 °C.

Hemi-1,5-naphthalenedisulphonate: melting point 260-265 °C.

Hydrogen sulphate: melting point 203-207 °C.

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

Hydrochloride: melting point: 104-108 °C.

Mesylate: melting point 141-145 °C.

Hemi-1,5-naphthalenedisulphonate: melting point 271-274 °C.

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

Hydrochloride: melting point: 101-107 °C.

Mesylate: melting point 168-173 °C.

Hemi-1,5-naphthalenedisulphonate: melting point: 159-164 °C.

Hydrogen sulphate: melting point 205-209 °C.

Example 6: 3-Methyl-butane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester

Hydrochloride: melting point: 110-115 °C.

Mesylate: melting point 122-127 °C.

Hemi-1,5-naphthalenedisulphonate: melting point 161-164 °C.

Example 7: 3,3-Dimethyl-butane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester

Hydrochloride: melting point: 112-119 °C.

Mesylate: melting point 160-167 °C.

Hemi-1,5-naphthalenedisulphonate: melting point 276-279 °C.

Example 8: Propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester

Hydrochloride: melting point: 185-189 °C.

Mesylate: melting point 111-114 °C.

Hemi-1,5-naphthalenedisulphonate: melting point 156-161 °C.

Hydrogen sulphate: melting point 203-209 °C.

Example 9: Carbonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester propyl ester

Hydrochloride: melting point: 99-108 °C.

Mesylate: melting point 110-115 °C.

Hemi-1,5-naphthalenedisulphonate: melting point 175-180 °C.

Example 10: Pyridine-3-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester

Mesylate: melting point 225-227 °C.

Hemi-1,5-naphthalenedisulphonate: melting point 168-172 °C

Preparation of Free Bases

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

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 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)

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 **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%

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 **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 title compound as a solid.

^1H 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)

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 **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%.

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 **5, 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%.

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 **5, Step A** (0.49 g, 1.20 mmol) was dissolved in dichloromethane (20 ml), cooled to 0 °C 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%

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%.

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).

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 **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 **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.

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 **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.

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 **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%

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 **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.

13) 4-{1-(2,4-dichlorophenyl)-4-methyl-3-[(piperidin-1-ylamino)carbonyl]-1*H*-pyrazol-5-yl}phenyl pyridine-3-sulfonate

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 the title compound as a 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.

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 **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 $(M+H)^+$.

15) 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 **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.

16) 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 **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.

17) 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 **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.

18) 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%

19) 5-Chlorothiophene-2-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester

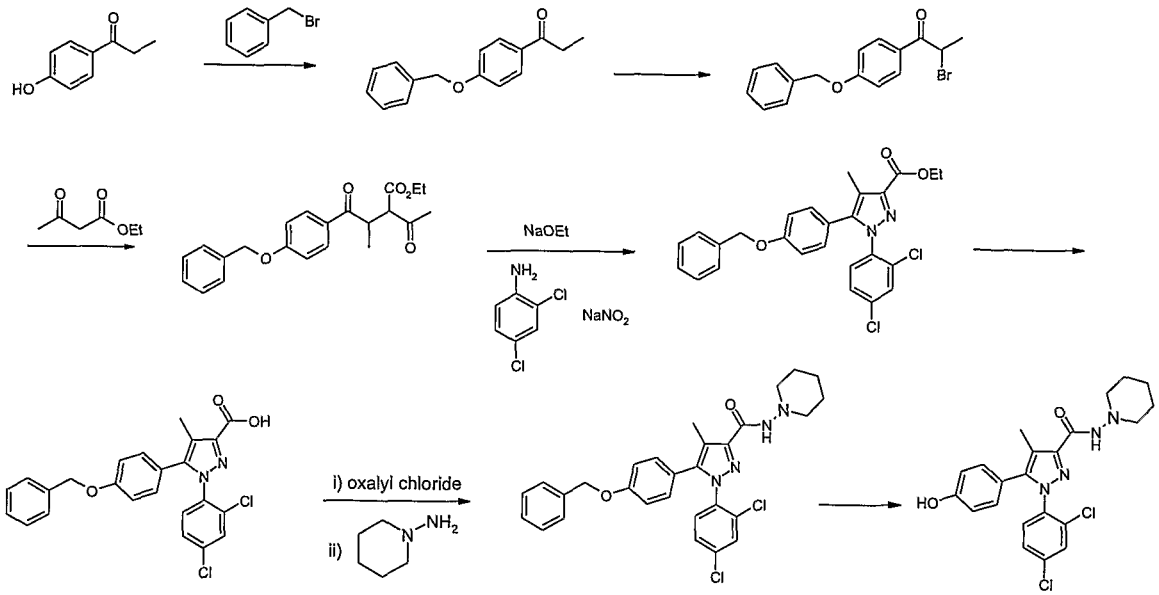
1-(2,4-Dichloro-phenyl)-5-(4-hydroxy-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide, prepared as in **1, Step F** (100 mg, 0.22 mmol) was dissolved in dry dichloromethane (3 ml) under nitrogen atmosphere and triethyl amine (0.09 ml) was added. 5-Chlorothiophene-2-sulfonyl chloride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

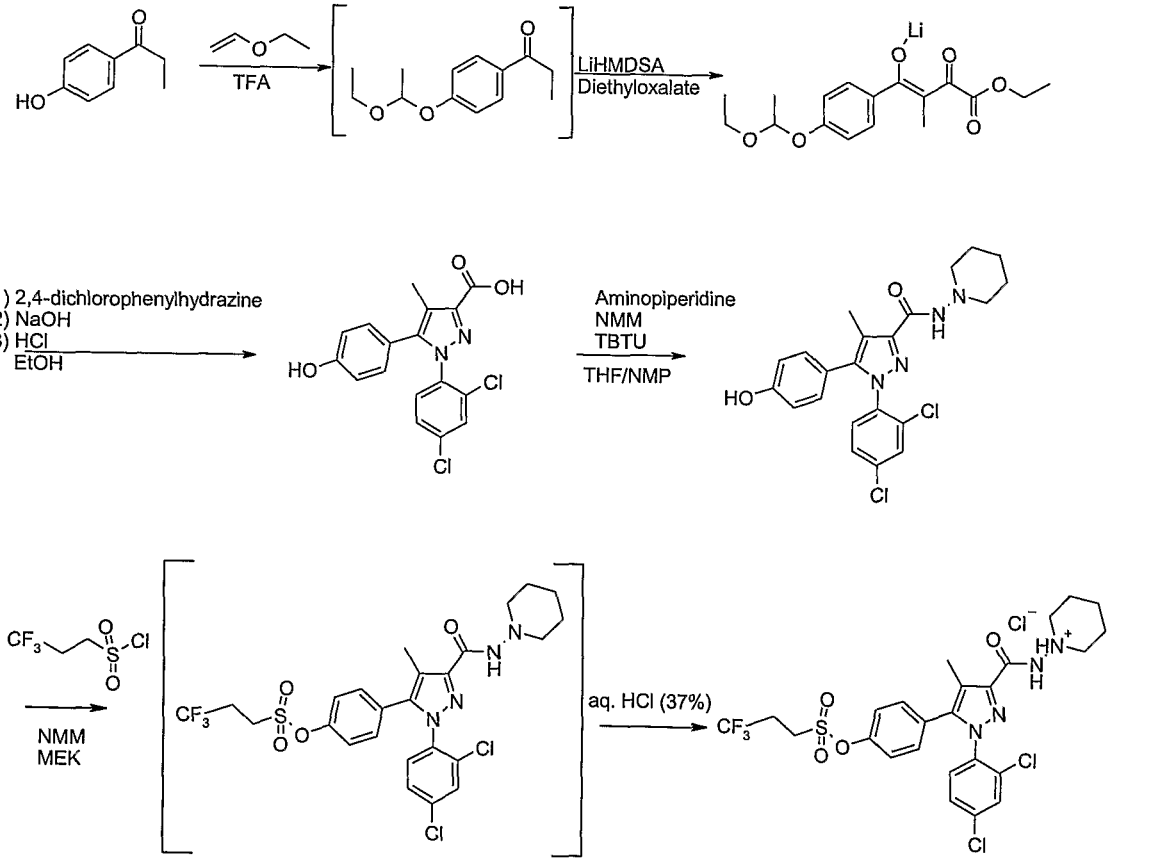
MS: 625 (M+1). HPLC: >99% purity.

GENERAL METHOD OF SYNTHESIS OF FREE BASES

Method A



Method B



Claims

1. A compound selected from:

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;

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;

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

in the form of a methanesulphonate salt, a hemi-1,5-naphthalenedisulphonate salt, a 1,2-ethanedisulfonic acid salt, a hydrochloride salt or a hydrogen sulphate salt but excluding pyridine-3-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hydrochloride.

2. One or more of the following:

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

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

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

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

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

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

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

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

4,4,4-trifluorobutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hydrogen sulphate;
propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]-2,6-difluorophenyl ester hydrochloride;
propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]-2,6-difluorophenyl ester mesylate;
propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]-2,6-difluorophenyl ester hemi-1,5-naphthalenedisulphonate;
3,3,3-trifluoropropane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hydrochloride;
3,3,3-trifluoropropane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester mesylate;
3,3,3-trifluoropropane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hemi-1,5-naphthalenedisulphonate;
3,3,3-trifluoropropane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hydrogen sulphate;
3-methylbutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hydrochloride;
3-methylbutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester mesylate;
3-methylbutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hemi-1,5-naphthalenedisulphonate;
3,3-dimethylbutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hydrochloride;
3,3-dimethylbutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester mesylate;
3,3-dimethylbutane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hemi-1,5-naphthalenedisulphonate;
propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester hydrochloride;
propane-1-sulfonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester mesylate;

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

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

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

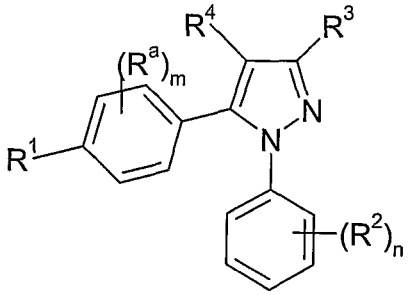
carbonic acid 4-[2-(2,4-dichlorophenyl)-4-methyl-5-(piperidin-1-ylcarbamoyl)-2H-pyrazol-3-yl]phenyl ester propyl ester mesylate;

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

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

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

3. A compound of formula I



I

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 $X\text{-}Y\text{-}NR^7R^8$

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 the form of a methanesulphonate salt, a hemi-1,5-naphthalenedisulphonate salt, or a 1,2-ethanedisulfonic acid salt.

4. A compound as claimed in any one of claims 1 to 3 for use as a medicament.

5. A pharmaceutical formulation comprising a compound as claimed in any one of claims 1 to 3 and a pharmaceutically acceptable adjuvant, diluent or carrier.

6. Use of a compound as claimed in any one of claims 1 to 3 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.

7. 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 as claimed in any one of claims 1 to 3 to a patient in need thereof.

8. A compound as defined in as claimed as claimed in any one of claims 1 to 3 for use in the treatment of obesity.