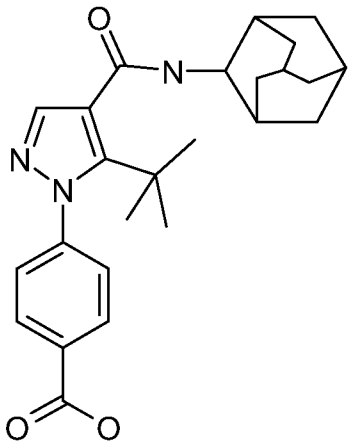
4-[4-(2-Adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid - 465

This invention relates to 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid (the Agent) and pharmaceutically-acceptable salts thereof and a particular crystalline form of the Agent (Form 1). The Agent possesses human 11-β-hydroxysteroid dehydrogenase type 1 enzyme (11βHSD1) inhibitory activity and accordingly has value in the treatment of disease states including metabolic syndrome and are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of the Agent, processes for the manufacture of a crystalline form of the Agent (Form 1), to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit 11βHSD1 in a warm-blooded animal, such as man.

The Agent is illustrated in Formula (I) hereinafter:



Glucocorticoids (cortisol in man, corticosterone in rodents) are counter regulatory hormones i.e. they oppose the actions of insulin (Dallman MF, Strack AM, Akana SF et al. 1993; Front Neuroendocrinol 14, 303-347). They regulate the expression of hepatic enzymes involved in gluconeogenesis and increase substrate supply by releasing glycerol from adipose tissue (increased lipolysis) and amino acids from muscle (decreased protein synthesis and increased protein degradation). Glucocorticoids are also important in the differentiation of pre-adipocytes into mature adipocytes which are able to store triglycerides (Bujalska IJ et al. 1999; Endocrinology 140, 3188-3196). This may be critical in disease states where glucocorticoids induced by "stress" are associated with central obesity which itself is a strong risk factor for type 2 diabetes, hypertension and cardiovascular disease (Bjorntorp P & Rosmond R 2000; Int. J. Obesity 24, S80-S85).

It is now well established that glucocorticoid activity is controlled not simply by secretion of cortisol but also at the tissue level by intracellular interconversion of active cortisol and inactive cortisone by the 11-beta hydroxysteroid dehydrogenases, 11βHSD1 (which activates cortisone) and 11βHSD2 (which inactivates cortisol) (Sandeep TC & Walker BR 2001 Trends in Endocrinol & Metab. 12, 446-453). That this mechanism may be important in man was initially shown using carbenoxolone (an anti-ulcer drug which inhibits both 11βHSD1 and 2) treatment which (Walker BR et al. 1995; J. Clin. Endocrinol. Metab. 80, 3155-3159) leads to increased insulin sensitivity indicating that 11βHSD1 may well be regulating the effects of insulin by decreasing tissue levels of active glucocorticoids (Walker BR et al. 1995; J. Clin. Endocrinol. Metab. 80, 3155-3159).

Clinically, Cushing's syndrome is associated with cortisol excess which in turn is associated with glucose intolerance, central obesity (caused by stimulation of pre-adipocyte differentiation in this depot), dyslipidaemia and hypertension. Cushing's syndrome shows a number of clear parallels with metabolic syndrome. Even though the metabolic syndrome is not generally associated with excess circulating cortisol levels (Jessop DS et al. 2001; J. Clin. Endocrinol. Metab. 86, 4109-4114) abnormally high 11βHSD1 activity within tissues would be expected to have the same effect. In obese men it was shown that despite having similar or lower plasma cortisol levels than lean controls, 11βHSD1 activity in subcutaneous fat was greatly enhanced (Rask E et al. 2001; J. Clin. Endocrinol. Metab. 1418-1421). Furthermore, the central fat, associated with the metabolic syndrome expresses much higher levels of 11βHSD1 activity than subcutaneous fat (Bujalska IJ et al. 1997; Lancet 349, 1210-1213). Thus there appears to be a link between glucocorticoids, 11βHSD1 and the metabolic syndrome.

11βHSD1 knock-out mice show attenuated glucocorticoid-induced activation of gluconeogenic enzymes in response to fasting and lower plasma glucose levels in response to stress or obesity (Kotelevtsev Y et al. 1997; Proc. Natl. Acad. Sci USA 94, 14924-14929) indicating the utility of inhibition of 11βHSD1 in lowering of plasma glucose and hepatic glucose output in type 2 diabetes. Furthermore, these mice express an anti-atherogenic lipoprotein profile, having low triglycerides, increased HDL cholesterol and increased apo-lipoprotein AI levels. (Morton NM et al. 2001; J. Biol. Chem. 276, 41293-41300). This phenotype is due to an increased hepatic expression of enzymes of fat

catabolism and PPARα. Again this indicates the utility of 11βHSD1 inhibition in treatment of the dyslipidaemia of the metabolic syndrome.

The most convincing demonstration of a link between the metabolic syndrome and 11βHSD1 comes from recent studies of transgenic mice over-expressing 11βHSD1 (Masuzaki H et al. 2001; Science 294, 2166-2170). When expressed under the control of an adipose specific promoter, 11βHSD1 transgenic mice have high adipose levels of corticosterone, central obesity, insulin resistant diabetes, hyperlipidaemia and hyperphagia. Most importantly, the increased levels of 11βHSD1 activity in the fat of these mice are similar to those seen in obese subjects. Hepatic 11βHSD1 activity and plasma corticosterone levels were normal, however, hepatic portal vein levels of corticosterone were increased 3 fold and it is thought that this is the cause of the metabolic effects in liver.

Overall it is now clear that the complete metabolic syndrome can be mimicked in mice simply by overexpressing 11βHSD1 in fat alone at levels similar to those in obese man.

11βHSD1 tissue distribution is widespread and overlapping with that of the glucocorticoid receptor. Thus, 11βHSD1 inhibition could potentially oppose the effects of glucocorticoids in a number of physiological/pathological roles. 11βHSD1 is present in human skeletal muscle and glucocorticoid opposition to the anabolic effects of insulin on protein turnover and glucose metabolism are well documented (Whorwood CB et al. 2001; J. Clin. Endocrinol. Metab. 86, 2296-2308). Skeletal muscle must therefore be an important target for 11βHSD1 based therapy.

Glucocorticoids also decrease insulin secretion and this could exacerbate the effects of glucocorticoid induced insulin resistance. Pancreatic islets express 11βHSD1 and carbenoxolone can inhibit the effects of 11-dehydocorticosterone on insulin release (Davani B et al. 2000; J. Biol. Chem. 275, 34841-34844). Thus in treatment of diabetes 11βHSD1 inhibitors may not only act at the tissue level on insulin resistance but also increase insulin secretion itself.

Skeletal development and bone function is also regulated by glucocorticoid action. 11βHSD1 is present in human bone osteoclasts and osteoblasts and treatment of healthy volunteers with carbenoxolone showed a decrease in bone resorption markers with no

change in bone formation markers (Cooper MS et al 2000; Bone 27, 375-381). Inhibition of 11βHSD1 activity in bone could be used as a protective mechanism in treatment of osteoporosis.

Glucocorticoids may also be involved in diseases of the eye such as glaucoma. 11βHSD1 has been shown to affect intraocular pressure in man and inhibition of 11βHSD1 may be expected to alleviate the increased intraocular pressure associated with glaucoma (Rauz S et al. 2001; Investigative Opthalmology & Visual Science 42, 2037-2042).

There appears to be a convincing link between 11βHSD1 and the metabolic syndrome both in rodents and in humans. Evidence suggests that a drug which specifically inhibits 11βHSD1 in type 2 obese diabetic patients will lower blood glucose by reducing hepatic gluconeogenesis, reduce central obesity, improve the atherogenic lipoprotein phenotype, lower blood pressure and reduce insulin resistance. Insulin effects in muscle will be enhanced and insulin secretion from the beta cells of the islet may also be increased.

Currently there are two main recognised definitions of metabolic syndrome.

1) The Adult Treatment Panel (ATP III 2001 JMA) definition of metabolic syndrome indicates that it is present if the patient has three or more of the following symptoms:
Waist measuring at least 40 inches (102 cm) for men, 35 inches (88 cm) for women;
Serum triglyceride levels of at least 150 mg/dl (1.69 mmol/l);
HDL cholesterol levels of less than 40 mg/dl (1.04 mmol/l) in men, less than 50 mg/dl (1.29 mmol/l) in women;
Blood pressure of at least 135/80 mm Hg; and / or Blood sugar (serum glucose) of at least 110 mg/dl (6.1 mmol/l).

2) The WHO consultation has recommended the following definition which does not imply causal relationships and is suggested as a working definition to be improved upon in due course:
The patient has at least one of the following conditions: glucose intolerance, impaired glucose tolerance (IGT) or diabetes mellitus and/or insulin resistance; together with two or more of the following:
Raised Arterial Pressure;
Raised plasma triglycerides
Central Obesity

Microalbuminuria

We have found that the Agent, or a pharmaceutically-acceptable salt thereof, is an effective 11βHSD1inhibitor, and accordingly has value in the treatment of disease states associated with metabolic syndrome. We have also found that the compound of the invention has improved properties, which would make it a better candidate for use as pharmaceuticals.

Accordingly the invention relates to 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid;

or a pharmaceutically-acceptable salt thereof.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

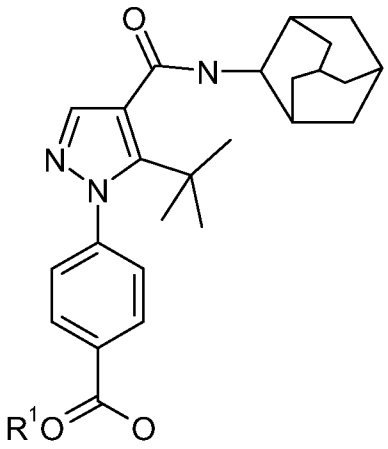
It is to be understood that the invention encompasses all such solvated forms, which possess 11βHSD1 inhibitory activity.

The invention also relates to in vivo hydrolysable esters of a compound of the Agent. In vivo hydrolysable esters are those esters that are broken down in the animal body to produce the parent carboxylic acid.

In one embodiment of the invention is provided 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid. In an alternative embodiment are provided pharmaceutically-acceptable salts of 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid.

Another aspect of the present invention provides a process for preparing the Agent or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (1)) comprises any one of processes a) or b):

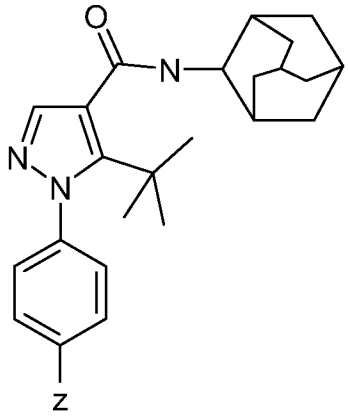
a) hydrolysis of an ester of formula (2):



(2)

wherein R^1 is an alkyl or aryl group; or

b) converting Z in a compound of the formula (3):



(3)

into a carboxy group, wherein Z is an functional group capable of conversion into a carboxylic acid;

and thereafter if necessary or desirable forming a pharmaceutically-acceptable salt thereof.

Suitable conditions for the above processes a) to b) are as follows.

Process a) may be carried out under either acidic or basic conditions dependant on the nature of the ester group (R^1) but typically may be carried out under basic conditions, for example with aqueous sodium hydroxide, using a suitable solvent such as methanol for example. Typically the reaction is carried out at ambient temperature, however some esters may require cleavage using Microwave or conventional heating, for example at temperatures between 30-100°C. Examples of suitable values for R^1 include methyl, ethyl, tert-butyl, phenyl, benzyl and paramethoxybenzyl, particularly methyl or ethyl.

An example of process b) is the conversion of an aryl halide into an aryl carboxylic acid through the use of metal-catalysed carbonylation. Examples of such processes are known to the art and are carried out in a suitable solvent such as ethanol/dioxane for example using a suitable catalyst, or combination of catalysts, for example, Herrmann's catalyst together with Fu's salt in the presence of a suitable source of carbon monoxide, for example, molybdenum hexacarbonyl or gaseous CO typically in the presence of a suitable base, or combination of bases for example DMAP/DIPEA. Typically the reaction is carried out at elevated temperature using Microwave or conventional heating, for example at temperatures between 100-180°C. It will be appreciated by those skilled in the art that the choice of solvent will depend on the nature of the product isolated, for example alcoholic solvents will tend to lead to isolation of the ester which may be subsequently cleaved on work-up of the reaction to give the appropriate acid. It will also be appreciated by those skilled in the art that compounds of formula (3) may be accessed by all of the methods used to describe the synthesis of compounds of formula (2).

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or

phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example hydroxylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Another aspect of the invention relates to a crystalline form of 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid (Form 1), which has an X-ray diffraction pattern with at least one specific peak at about 2-theta = 16.8.

The 2-theta (θ) values were measured using CuKa radiation.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with at least two specific peaks at about 2-theta = 16.8 ^{o} and 18.5^{o}.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 16.8, 18.5 and 14.4°.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 16.8, 18.5, 14.4, 13.9 and 19.8°.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 16.8, 18.5, 14.4, 13.9, 19.8, 20.1, 15.8, 22.6, 19.4 and 20.4°.

According to the present invention there is provided crystalline form, Form 1 which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern, using CuKa radiation, shown in Figure 1.

According to the present invention there is provided crystalline form, Form 1, which has an X-ray powder diffraction pattern with at least one specific peak at 2-theta = ° plus or minus 0.5° 2-theta.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with at least one specific peak at 2-theta = 16.8° plus or minus 0.5° 2-theta.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with at least two specific peaks at 2-theta = 16.8° and 18.5° wherein said values may be plus or minus 0.5° 2-theta.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with specific peaks at 2-theta = 16.8, 18.5 and 14.4° wherein said values may be plus or minus 0.5° 2-theta.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with specific peaks at 2-theta = 16.8, 18.5, 14.4, 13.9 and 19.8° wherein said values may be plus or minus 0.5° 2-theta.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with specific peaks at 2-theta = 16.8, 18.5, 14.4, 13.9, 19.8, 20.1, 15.8, 22.6, 19.4 and 20.4° wherein said values may be plus or minus 0.5° 2-theta.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with at least one specific peak at 2-theta = 16.8°.

According to the present invention there is provided a crystalline form, Form 1, which has an X-ray powder diffraction pattern with at least two specific peaks at 2-theta = 16.8 and 18.5 °.

According to the present invention there is provided crystalline form, Form 1, which has an X-ray powder diffraction pattern with specific peaks at 2-theta = 16.8, 18.5 and 14.4°.

According to the present invention there is provided crystalline form, Form 1, which has an X-ray powder diffraction pattern with specific peaks at 2-theta = 16.8, 18.5, 14.4, 13.9 and 19.8°.

According to the present invention there is provided crystalline form, Form 1, which has an X-ray powder diffraction pattern with specific peaks at 2-theta = 16.8, 18.5, 14.4, 13.9, 19.8, 20.1, 15.8, 22.6, 19.4 and 20.4°.

According to the present invention there is provided crystalline form, Form 1, which has an X-ray powder diffraction pattern, using CuKa radiation, as shown in Figure 1.

Table A

Ten most Prominent X-Ray Powder Diffraction peaks for 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid (Form 1)

Angle 2-Theta (2θ)	Intensity %	Relative Intensity
16.845	100.0	vs
18.511	65.9	vs
14.408	36.5	vs
13.874	23.8	s
19.772	23.2	s
20.105	18.3	s
15.758	16.4	s

22.621	15.0	s
19.400	14.6	s
24.408	14.5	s

vs = very strong

s = strong

DSC analysis shows Form 1 has an onset of melting at 308.8°C and a peak at 310.5°C. The DCS thermogram is depicted in Figure 2.

When it is stated that the present invention relates to a crystalline form of Form 1, the degree of crystallinity is conveniently greater than about 60%, more conveniently greater than about 80%, preferably greater than about 90% and more preferably greater than about 95%. Most preferably the degree of crystallinity is greater than about 98%.

The Form 1 provides X-ray powder diffraction patterns substantially the same as the X-ray powder diffraction patterns shown in Figure 1 and has substantially the ten most prominent peaks (angle 2-theta values) shown in Table A. It will be understood that the 2-theta values of the X-ray powder diffraction pattern may vary slightly from one machine to another or from one sample to another, and so the values quoted are not to be construed as absolute.

It is known that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment or machine used). In particular, it is generally known that intensities in an X-ray powder diffraction pattern may fluctuate depending on measurement conditions. Therefore it should be understood that the Form 1 of the present invention is not limited to the crystals that provide X-ray powder diffraction patterns identical to the X-ray powder diffraction pattern shown in Figure 1, and any crystals providing X-ray powder diffraction patterns substantially the same as those shown in Figure 1 fall within the scope of the present invention. A person skilled in the art of X-ray powder diffraction is able to judge the substantial identity of X-ray powder diffraction patterns.

Persons skilled in the art of X-ray powder diffraction will realise that the relative intensity of peaks can be affected by, for example, grains above 30 microns in size and non-unitary aspect ratios, which may affect analysis of samples. The skilled person will also realise that the position of reflections can be affected by the precise height at which

the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence the diffraction pattern data presented are not to be taken as absolute values. (Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons 1996; Bunn, C.W. (1948), Chemical Crystallography, Clarendon Press, London; Klug, H. P. & Alexander, L. E. (1974), X-Ray Diffraction Procedures).

Generally, a measurement error of a diffraction angle in an X-ray powder diffractogram is about 5% or less, in particular plus or minus 0.5° 2-theta, and such degree of a measurement error should be taken into account when considering the X-ray powder diffraction pattern in Figure 1 and when reading Tables A. Furthermore, it should be understood that intensities might fluctuate depending on experimental conditions and sample preparation (preferred orientation).

Details of Techniques Used

X-Ray Powder Diffraction

Table B

% Relative Intensity*	Definition
25 - 100	vs (very strong)
10 - 25	s (strong)
3 - 10	m (medium)
1 - 3	w (weak)

* The relative intensities are derived from diffractograms measured with fixed slits Analytical Instrument: Siemens D5000.

The X-ray powder diffraction spectra were determined by mounting a sample of the crystalline material on a Siemens single silicon crystal (SSC) wafer mount and spreading out the sample into a thin layer with the aid of a microscope slide. The sample was spun at 30 revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40kV and 40mA with a wavelength of 1.5406 angstroms. The collimated X-ray source was passed through an automatic variable divergence slit set at V20 and the reflected radiation directed through a 2mm antiscatter slit and a 0.2mm detector slit. The sample was exposed for 1 second per 0.02 degree 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-

theta in theta-theta mode. The running time was 31 minutes and 41 seconds. The instrument was equipped with a scintillation counter as detector. Control and data capture was by means of a Dell Optiplex 686 NT 4.0 Workstation operating with Diffract+ software. Persons skilled in the art of X-ray powder diffraction will realise that the relative intensity of peaks can be affected by, for example, grains above 30 microns in size and non-unitary aspect ratios that may affect analysis of samples. The skilled person will also realise that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence the diffraction pattern data presented are not to be taken as absolute values.

Differential Scanning Calorimetry

Analytical Instrument: TA Instruments Q1000 DSC.

Typically less than 5mg of material contained in a 40µl aluminium pan fitted with a lid was heated over the temperature range 25°C to 325°C at a constant heating rate of 10°C per minute. A purge gas using nitrogen was used - flow rate 100ml per minute.

As stated hereinbefore the Agent possesses 11βHSD1 inhibitory activity. These properties may be assessed using the following assay.

Assays

The conversion of cortisone to the active steroid cortisol by 11βHSD1 oxo-reductase activity, can be measured using a competitive homogeneous time resolved fluorescence assay (HTRF) (CisBio International, R&D, Administration and Europe Office, In Vitro Technologies — HTRF® / Bioassays BP 84175, 30204 Bagnols/Cèze Cedex, France. Cortisol bulk HTRF kit: Cat No. 62CORPEC).

The evaluation of the compound described herein was carried out using a baculovirus expressed N terminal 6-His tagged full length human 11βHSD1 enzyme(*1). The enzyme was purified from a detergent solublised cell lysate, using a copper chelate column. Inhibitors of 11βHSD1 reduce the conversion of cortisone to cortisol, which is identified by an increase in signal, in the above assay.

The compound to be tested was dissolved in dimethyl sulphoxide (DMSO) to 10mM and diluted further in assay buffer containing 1% DMSO to 10 fold the final assay concentration. Diluted compound was then plated into black 384 well plates (Matrix, Hudson NH, USA).

The assay was carried out in a total volume of 20µl consisting of cortisone (Sigma, Poole, Dorset, UK, 160nM), glucose-6-phosphate (Roche Diagnostics, 1mM), NADPH (Sigma, Poole, Dorset, 100µM), glucose-6-phosphate dehydrogenase (Roche Diagnostics, 12.5µg/ml), EDTA (Sigma, Poole, Dorset, UK, 1mM), assay buffer (K_2HPO_4/KH_2PO_4, 100mM) pH 7.5, recombinant 11βHSD1 [using an appropriate dilution to give a viable assay window – an example of a suitable dilution may be 1 in 1000 dilution of stock enzyme] plus test compound. The assay plates were incubated for 25 minutes at 37°C after which time the reaction was stopped by the addition of 10µl of 0.5mM glycerrhetinic acid plus conjugated cortisol(XL665 or D2). 10µl of anti-cortisol Cryptate was then added and the plates sealed and incubated for 6 hours at room temperature. Fluorescence at 665nm and 620nm was measured and the 665nm:620nm ratio calculated using an Envision plate reader.

These data were then used to calculate IC_{50} values for each compound (Origin 7.5, Microcal software, Northampton MA, USA) and/or the % inhibition at 30µM of compound.

*1 The Journal of Biological Chemistry, Vol. 26, No 25, pp16653 – 16658

The following results were obtained: Example 1 IC50 0.008 µM.

The oral bioavailability of the compound of the invention may be tested as follows:

Determination of Bioavailability in PK Studies

Compounds are dosed intravenously at 2mg/kg (2ml/kg) and orally at 5mg/kg (5ml/kg) in a 25% HPBCD in sorrensons buffer pH 5.5 formulation. Blood samples (200ul) are taken Predose, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8 and 24 h post dose for both routes and plasma prepared by centrifugation. Plasma samples are analysed as below. PK parameters (clearance, volume of distribution, bioavailability, fraction absorbed etc.) are calculated by standard PK methods using suitable PK software (WinNon-Lin).

Bioanalysis of plasma samples

The guidelines described are for the manual preparation of plasma samples following single compound or cassette dosing of project compounds to all PK species used within

discovery DMPK. Analysis by open access (LC-MS/MS) or manual approaches (LC-MS) is described.

Contents

1. Materials
2. Generic Extraction Method
3. Example Sample List Using Generic Plate Layout
4. Open Access Batch Submission and System Checks
5. Acceptance Criteria for Batch Pass

1. Materials

Solvents: Methanol, acetonitrile and DMSO

Water: Purified or HPLC grade

1ml shallow 96-well plates OR eppendorf tubes

2ml deep well 96-well plates plus lids

Blank (control) plasma

2. Generic Extraction Method

Solubilise compound(s) to 1mg/ml using DMSO taking into account salt factors if any.

The DMSO stock(s) may be used to make all calibration & quality control (QC) samples:

2.i Single compound analysis

2.i.a Preparation of calibration and QC samples:

1. Prepare standard solutions as follows:

Stock diluted ng/ml	Volume methanol ml	Volume stock ml	Standard conc. ng/ml	Post plasma dilution conc. ng/ml
1mg/ml	0.9	0.1	100,000	10,000
100,000	0.5	0.5	50,000	5,000
50,000	0.75	0.5	20,000	2,000
20,000	0.5	0.5	10,000	1,000
10,000	0.5	0.5	5,000	500
5,000	2	0.5	1,000	100
1,000	0.5	0.5	500	50
500	0.75	0.5	200	20
200	0.5	0.5	100	10

Stock diluted	Volume methanol	Volume stock	Standard conc.	Post plasma dilution conc.
100	0.5	0.5	50	5
50	0.5	0.5	10	1

2. Transfer 50ul blank plasma to a well of a 1ml 96-well plate (shallow well)
3. Transfer 5ul of each of the standard solutions to further wells of the plate
4. Add 50ul blank plasma to each of these wells.
5. To generate the QC samples, add three aliquots of 5ul of the 100ng/ml, 1000ng/ml and 10,000ng/ml standard solutions to the plate (3 QCs at each concentration).
6. Add 50ul blank plasma to each of these.
7. Transfer 50ul of each PK sample to the 1ml 96-well plate
8. Add 5ul methanol (- compound) to each of the PK samples
9. Ensure all dose formulations are well mixed by vortex mixing.
10. Dilute intravenous (IV) and oral dose (PO) formulations of expected concentration to 10ug/ml in methanol. (For example, a formulation made to an expected concentration of 2 mg/ml would be diluted 1:200 to give 10ug/ml solution).
11. Add 6x 50 ul aliquots of plasma to the plate. Add 5 ul of diluted IV formulation to three of the wells, repeat with PO formulation and remaining 3 wells.
12. Precipitate proteins by adding 100ul acetonitrile containing a project related internal standard (at 1ug/ml) to all calibration, QC, PK and formulation samples.
13. Vortex mix the plate before centrifugation at 4,000g for 10 minutes.
14. Transfer 100ul of the supernatant to the wells of a 2ml 96-well plate (see following plate map). Care should be taken not to disturb the pellet.
15. Add ~1.5ml of 50:50 Methanol: Water into the last well.
16. For analysis on triple quad systems: add 400ul water (HPLC grade) to each sample. Gently mix.
17. Add 100ul of the 100,000ng/ml stock of each of the standard solutions to the 2ml plate and add 900ul water. Add a sample of internal standard to a further well (see plate map). *These are for compound tuning (denoted on the plate map as tune solutions)*
18. For analysis on platform systems: add 100ul water (HPLC grade) to each sample. Gently mix.

19. Manually tune all compounds using compound solutions prepared to 5,000ng/ml (add 100ul of the 50,000ng/ml standard solutions to 900ul water)

2.ii Cassette dose analysis

2.iia Preparation of calibration and QC samples:

Note: For cassette dosing, the amount of methanol required to dilute the 1mg/ml stock will be adjusted according to the number of compounds present.

1. Add 100ul of each 1mg/ml stock required to a vial.
2. Add the required volume of methanol to yield a total volume of 1ml.
3. Perform all further steps as for single compound analysis (steps 2 –16 above).

2.iii In cases where PK samples exceed the Upper limit of Quantification (ULOQ).

1. Prepare a further calibration curve and QC samples as above (steps 1 – 6).
2. Transfer <50ul (e.g. 25ul) of the PK samples that exceed the ULOQ.
3. Add enough control plasma to these samples to yield a final plasma volume of 50ul. Make a note of the dilution made.
4. Transfer 50ul of all remaining PK samples.
5. Prepare all formulation samples and extract all samples as described above. (steps 8 – 16)

Note: Upper concentrations used to generate the calibration curve may be reviewed, however, care must be taken to avoid saturation of the HPLC column or MS equipment. It is for this reason that dilution of PK samples is recommended.

2.iv In cases of poor sensitivity (high Lower Limit of Quantification).

Note: High LLOQ is taken as when most of the plasma concentrations lie below the lower limit of quantification or where the LLOQ is greater the 10ng/ml. The following methods should be applied when either of these scenarios is encountered.

According to a further aspect of the invention there is provided a pharmaceutical composition, which comprises the Agent, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration

by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing). In general, compositions in a form suitable for oral use are preferred.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically-acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as

polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures

using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

We have found that the Agent, or a pharmaceutically-acceptable salt thereof, is an effective 11βHSD1inhibitor, and accordingly has value in the treatment of disease states associated with metabolic syndrome.

It is to be understood that where the term "metabolic syndrome" is used herein, this relates to metabolic syndrome as defined in 1) and/or 2) or any other recognised definition of this syndrome. Synonyms for "metabolic syndrome" used in the art include Reaven's Syndrome, Insulin Resistance Syndrome and Syndrome X. It is to be understood that where the term "metabolic syndrome" is used herein it also refers to Reaven's Syndrome, Insulin Resistance Syndrome and Syndrome X.

According to a further aspect of the present invention there is provided the Agent, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

Thus according to this aspect of the invention there is the Agent, or a pharmaceutically-acceptable salt thereof, for use as a medicament.

According to another feature of the invention there is provided the use of the Agent, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for use in the production of an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the Agent, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for use in the production of an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man.

Where production of or producing an 11βHSD1 inhibitory effect is referred to suitably this refers to the treatment of metabolic syndrome. Alternatively, where production of an 11βHSD1 inhibitory effect is referred to this refers to the treatment of diabetes, obesity, hyperlipidaemia, hyperglycaemia, hyperinsulinemia or hypertension, particularly type 2 diabetes and obesity. Alternatively, where production of an 11βHSD1 inhibitory effect is referred to this refers to the treatment of glaucoma, osteoporosis, tuberculosis, dementia, cognitive disorders or depression.

Alternatively, where production of an 11βHSD1 inhibitory effect is referred to this refers to the treatment of cognitive disorders, such as improving the cognitive ability of an individual, for example by improvement of verbal fluency, verbal memory or logical memory, or for treatment of mild cognitive disorders. See for example WO03/086410 and references contained therein, and Proceedings of National Academy of Sciences (PNAS), 2001, 98(8), 4717-4721.

Alternatively, where production of an 11βHSD1 inhibitory effect is referred to this refers to the treatment of, delaying the onset of and/or reducing the risk of atherosclerosis – see for example J. Experimental Medicine, 2005, 202(4), 517-527.

Alternatively, where production of an 11βHSD1 inhibitory effect is referred to this refers to the treatment of Alzheimers and/or neurodegenerative disorders.

According to a further feature of this aspect of the invention there is provided a method for producing an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1), or a pharmaceutically-acceptable salt thereof.

In addition to their use in therapeutic medicine, the Agent, or a pharmaceutically-salt thereof, are also useful as pharmacological tools in the development and standardisation of in vitro and *in vivo* test systems for the evaluation of the effects of inhibitors of 11βHSD1 in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The inhibition of 11βHSD1 described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example agents than might be co-administered with 11βHSD1 inhibitors, particularly those of the present invention, may include the following main categories of treatment:

1) Insulin and insulin analogues;

2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide), prandial glucose regulators (for example repaglinide, nateglinide), glucagon-like peptide 1 agonist (GLP1 agonist) (for example exenatide, liraglutide) and dipeptidyl peptidase IV inhibitors (DPP-IV inhibitors);

3) Insulin sensitising agents including PPARγ agonists (for example pioglitazone and rosiglitazone);

4) Agents that suppress hepatic glucose output (for example metformin);

5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);

6) Agents designed to treat the complications of prolonged hyperglycaemia; e.g. aldose reductase inhibitors

7) Other anti-diabetic agents including phosotyrosine phosphatase inhibitors, glucose 6 - phosphatase inhibitors, glucagon receptor antagonists, glucokinase activators, glycogen phosphorylase inhibitors, fructose 1,6 bisphosphastase inhibitors, glutamine:fructose -6-phosphate amidotransferase inhibitors

8) Anti-obesity agents (for example sibutramine and orlistat);

9) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); ileal bile acid absorption inhibitors (IBATi), cholesterol ester transfer protein inhibitors and nicotinic acid and analogues (niacin and slow release formulations);

10) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); calcium antagonists (eg. nifedipine); angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);

11) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors; antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;

12) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone); and

13) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors).

The invention also relates to pharmaceutical compositions, combinations, medical uses and methods of treatment of the Agent (Form 1) as for the Agent hereinabove described.

Examples

The invention will now be illustrated by the following Example in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C and under an atmosphere of an inert gas such as argon;

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pa; 4.5-30 mmHg) with a bath temperature of up to 60 °C;

(iii) chromatography means flash chromatography on silica gel;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields are given for illustration only and are not necessarily those which can be

obtained by diligent process development; preparations were repeated if more material was required;

(vi) where given, NMR data (^{1}H) is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS), determined at 300 or 400 MHz (unless otherwise stated) using perdeuterio dimethyl sulfoxide (DMSO-d_6) as solvent, unless otherwise stated; peak multiplicities are shown thus: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in volume : volume (v/v) terms;

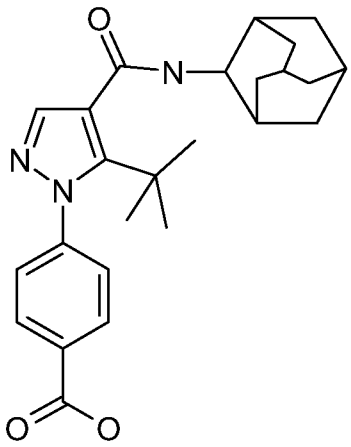
(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported;

(x) The following abbreviations may be used below or in the process section hereinbefore:

Et_2O	diethyl ether
DMF	dimethylformamide
DCM	dichloromethane
THF	tetrahydrofuran
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
MTBE	methyl tert-butyl ether
DSC	differential scanning calorimetry

Example 1

4-[4-(2-Adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid



2M aqueous sodium hydroxide solution (51.7 mL, 103.32 mmol) was added to methyl 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoate **(Intermediate 1)** (4.5 g, 10.33 mmol) in methanol (100 mL). The mixture was stirred at 70 °C for 1 hour and then cooled to ambient temperature, concentrated under reduced pressure and diluted with water (100 mL). The reaction mixture was adjusted to pH 3 with 2M HCl. The reaction mixture was extracted with EtOAc (500 mL) and washed sequentially with water (2x100 mL), and saturated brine (50 mL). The organic layer was dried over MgSO4, filtered and evaporated to give a pale yellow solid. The solid was washed with EtOAc (20mL), collected by filtration and dried under vacuum to give 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid (3.89 g, 89 %) as a cream crystalline solid.

1H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (9H, s), 1.49 (2H, d), 1.70-1.96 (10H, m), 2.09 (2H, d), 3.98 - 4.01 (1H, m), 7.49 - 7.53 (2H, m), 7.61 (1H, s), 8.06 - 8.09 (2H, m), 8.20 (1H, d), 13.30 (1H, s)

m/z (ESI+) (M+H)+ = 422

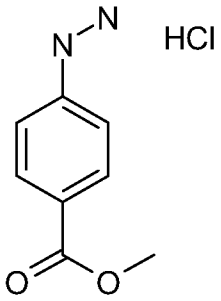
m.p. 308.8°C (onset)

Example 1 may also be prepared as follows:

Aqueous sodium hydroxide (2M) (2.5 eq) was added portionwise over 5 minutes to a stirred suspension of methyl 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoate **(Intermediate 1)** (1.0 eq) in methanol (10 vol) at 20°C (exotherm 20 - 27°C). The resulting suspension was heated to 70°C (jacket temperature), (batch refluxes approx

60-65°C) for 1 hour (complete by LCMS). The orange reaction mixture was cooled to 20°C (solution remained slightly cloudy) and filtered through celite to remove a small amount of solids. The filtrate was then poured into a flange flask and water (25 vol) was added. The mixture was then adjusted to pH 3 with 2M HCl (approx 800-850ml) (turns very thick). The aqueous was then filtered and the pale yellow solid washed with water, sucked dry overnight, and washed with acetonitrile and finally 1:1 acetonotrile/diethyl ether and dried under vacuum at 50°C for 72 hours (weekend) to give 4-[4-(2-adamantylcarbamoyl)-5-tertbutyl-pyrazol-1-yl]benzoic acid (80 %) as a solid.

Intermediate 2: methyl 4-hydrazinylbenzoate hydrochloride



Hydrogen chloride 4M in Dioxan (100 mL, 399.60 mmol) was added to 4-Hydrazinobenzoic acid (15.2 g, 99.90 mmol) in MeOH (200 mL) . The resulting suspension was stirred at 90 °C for 5 hours. After cooling to 20°C the precipitate was collected by filtration, washed with Et2O (100 mL) and dried under vacuum to afford 2-(4-(methoxycarbonyl)phenyl)hydrazinium chloride (16.50 g, 82 %) as a cream crystalline solid.

m/z (ESI-) (M-H)- = 165; HPLC t_R = 1.12 min.

1H NMR (400.13 MHz, DMSO-d6) δ 3.81 (3H, s), 6.99 - 7.02 (2H, m), 7.86 - 7.90 (2H, m), 8.98 (1H, s), 10.47 (3H, s)

Intermediate 2 may also be prepared as follows:

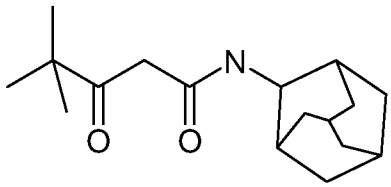
Methanolic hydrochloric acid solution (4M) (4 equiv., freshly prepared) was added to a suspension of 4-hydrazinobenzoic acid (1 equiv.) in methanol (12.6 vols.), under nitrogen.

The mixture was stirred under reflux for three hours and then cooled to below 15 °C. The solid was collected by filtration, washed with MTBE (6.5 vols.) and dried in air to give the product as a solid.

TLC DCM : MeOH, 9 : 1, Produt R_f 0.87

mp 233.8 – 234.6 °C

Intermediate 3: N-(2-adamantyl)-4,4-dimethyl-3-oxo-pentanamide



A 1M solution of solution of lithium bis(trimethylsilyl)amide in THF (22.84 ml, 22.84 mmol) was added to THF (25mL) and cooled under nitrogen to -78°C. A solution of 3,3-dimethyl-2-butanone (2.287 g, 22.84 mmol) in THF (25mL) was added drop wise over a period of 5 minutes. The resulting solution was stirred at -78 °C under nitrogen for 15 minutes. A solution of 2-isocyanatoadamantane *(prepared from 2-adamantylamine hydrochloride by the method of R.Reck & C.Jochims Chem. Ber. 115(1982) p864)* (3.68 g, 20.76 mmol) in THF (20mL) was added over a period of 5 minutes. The resulting solution was stirred at -78 °C for 1 hour and then allowed to warm to 20°C over 1h. The reaction mixture was poured into saturated NH_4Cl (150 mL) and extracted with EtOAc (2 x 100 mL), the organic layer was washed with water (50mL) and brine (50mL) dried over MgSO4, filtered and evaporated to afford a yellow oil.The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford N-(2-adamantyl)-4,4-dimethyl-3-oxo-pentanamide (4.64 g, 81 %) as a white solid.

1H NMR (400.13 MHz, DMSO-d_6) δ 1.08 - 1.09 (9H, m), 1.50 (2H, d), 1.66 - 1.89 (10H, m), 1.95 - 2.00 (2H, m), 3.53 (1.4H, s), 3.80 - 3.94 (1H, m), 5.30 (0.3H, s), 7.77- 7.87 (1H, m), 14.43 (0.3H, s) (2:1 mixture of keto and enol forms)

m/z (ESI+) $(M+H)^+$ = 278

Intermediate 3 may also be prepared as follows:

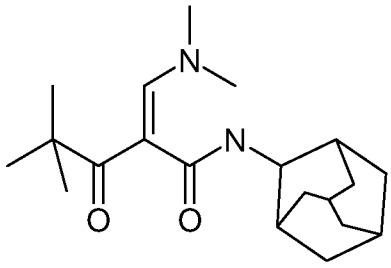
Aqueous sodium hydroxide solution (3M) (5 vols.) was added to a stirred suspension of 2-adamantylamine hydrochloride (1 equiv.) in water (5 vols.). DCM (5 vols.) was added to the resulting thick suspension and the phases separated. The aqueous was extracted with DCM (4 x 5 vols.) and the combined organics concentrated to give the free amine as a white solid.

Ethyl pivaloylacetate (1 equiv.) was added to a suspension of the free amine in xylenes (6.5 vols.), under nitrogen, and the mixture stirred under reflux for 6.5 hours. The batch was cooled to room temperature and concentrated to dryness. The residue was purged with toluene (3 x 1 vol.) followed by hexane (3 x 1 vol.). The resulting solid was digested in hexane at 50 °C for five minutes and then cooled to room temperature. The white solid was filtered, washed with hexane (2 vols.) and dried in air.

TLC Hexane : EtOAc, 1 : 1, Product R_f 0.66

mp 124.5 – 125.1 °C

Intermediate 4: (2)-N-(2-adamantyl)-2-(dimethylaminomethylidene)-4,4-dimethyl-3-oxo-pentanamide



N,N-Dimethylformamide dimethyl acetal (3.02 mL, 22.71 mmol) was added to a stirred suspension of N-(2-adamantyl)-4,4-dimethyl-3-oxo-pentanamide **(Intermediate 3)** (5.25 g, 18.93 mmol) in 1,4-dioxane (50 mL) under nitrogen. The resulting mixture was stirred at 100 °C for 2 hours. The reaction mixture was evaporated to dryness and the resulting pale cream solid was dried under vacuum to afford (2)-N-(2-adamantyl)-2-(dimethylaminomethylidene)-4,4-dimethyl-3-oxo-pentanamide (5.83 g, 93 %).

1H NMR (400.13 MHz, DMSO-d_6) δ 1.13 (9H, s), 1.47 (2H, d), 1.69 - 1.83 (10H, m), 2.03 (2H, d), 2.92 (6H, s), 3.90 (1H, d), 7.24 (1H, s), 7.94 (1H, d)

m/z (ESI+) (M+H)+ = 333

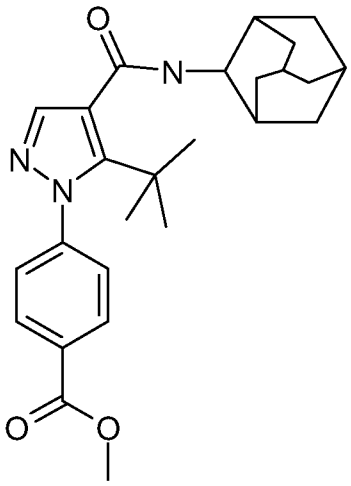
Intermediate#4 may also be prepared as follows:

N,N-Dimethylformamide dimethyl acetal (1.2 equivs.) was added to a solution of *N*-(2-adamantyl)-4,4-dimethyl-3-oxo-pentanamide **(Intermediate 3)** (1 equiv.) in 1,4-dioxane (9.6 vols.) under nitrogen. The mixture was heated under reflux for five hours and then cooled to room temperature. The solvent was removed *in vacuo* and the pale yellow solid used directly in the next stage.

TLC Hexane : EtOAc, 1 : 1, Product R_f 0.94 (impurities: R_f 0.06 + 0.66)

mp 143.6 – 147.6 °C

Intermediate 1: methyl 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoate



Methyl 4-hydrazinylbenzoate hydrochloride **(Intermediate 2)** (3.04 g, 15.00 mmol) was added in one portion to (2)-N-(2-adamantyl)-2-(dimethylaminomethylidene)-4,4-dimethyl-3-oxo-pentanamide **(Intermediate 4)** (4.99 g, 15 mmol) in ethanol (100 mL). 5 drops of acetic acid were added and the resulting solution was stirred at 80 °C for 2 hours. The reaction mixture was concentrated and diluted with EtOAc (500 mL), and washed sequentially with water (200 mL), and saturated brine (200 mL). The organic layer was dried over MgSO4, filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoate (4.66 g, 71.3 %) as a yellow solid.

1H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (9H, s), 1.50 (2H, d), 1.69-1.95 (10H, m), 2.09 (2H, d), 3.91 (3H, s), 3.99 (1H, d), 7.53 - 7.56 (2H, m), 7.62 (1H, s), 8.09 - 8.12 (2H, m), 8.20 (1H, d)

m/z (ESI+) (M+H)+ = 436

Intermediate# 1 may also be prepared as follows:

2-(4-(Methoxycarbonyl)phenyl)hydrazinium chloride **(Intermediate 2)** (1 equiv.) and then acetic acid (0.023 equivs.) were added to a solution of (2*Z*)-*N*-(2-adamantyl)-2-

(dimethylamino-methylidene)-4,4-dimethyl-3-oxo-pentanamide **(Intermediate 4)** (1 equiv.) in methanol (200 vols.), under nitrogen. The mixture stirred under reflux for 1.5 hours, cooled, concentrated to below 3.5 vols. and the resulting suspension diluted with ethyl acetate (96 vols.). The suspension was washed with water (34.4 vols.) giving a solution which was washed with brine (34.4 vols.), dried ($MgSO_4$) and concentrated to dryness. The crude product was slurried in MTBE (9 vols.) and stirred for 15 minutes. The pale yellow solid was filtered, washed with MTBE (11.4 vols.) and dried under vacuum at 60 °C.

TLC DCM : MeOH, 9 : 1, Product R_f 0.86 (trace impurity R_f 0.68)

mp 193.6 – 194.5 °C

Claims

1. The compound 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid; and pharmaceutically-acceptable salts thereof.

2. A crystalline form of 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid as claimed in claim 1.

3. A crystalline compound according to claim 2 having an X-ray powder diffraction pattern with peaks at the following 2-theta values measured using CuKa radiation: 16.8° and 18.5°.

4. A crystalline form of a compound according to claim 2 having an X-ray powder diffraction pattern with peaks at the following 2-theta values measured using CuKa radiation: 16.8°, 18.5° and 14.4°.

5. A crystalline form of a compound according to claim 2 having an X-ray powder diffraction pattern with peaks at the following 2-theta values measured using CuKa radiation: 16.8°, 18.5°, 14.4°, 13.9 and 19.8.

6. A crystalline compound as claimed in claim 2 having an X-ray diffraction pattern, using CuKa radiation, substantially the same as shown in Figure 1.

7. A crystalline form of 4-[4-(2-adamantylcarbamoyl)-5-tert-butyl-pyrazol-1-yl]benzoic acid having a melting point of about 308.8°C (onset).

8. A pharmaceutical composition, which comprises a compound according to any one of claims 1 to 7 in association with a pharmaceutically-acceptable diluent or carrier.

9. A compound according to any one of claims 1 to 7 for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

10. A compound according to any one of claims 1 to 7 for use as a medicament.

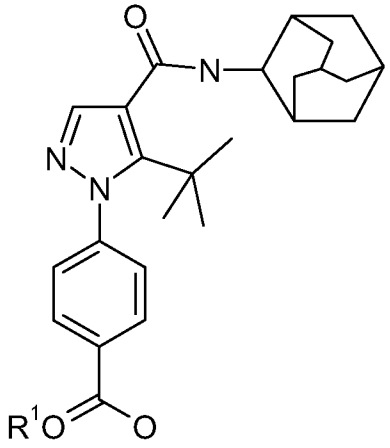
11. A compound according to any one of claims 1 to 7 in the manufacture of a medicament for use in the production of an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man.

12. A method of producing a 11βHSD1 inhibitory effect by administering an effective amount of a compound according to any one of claims 1 to 7 to a mammal in need of such treatment.

13. A method according to claim 12 wherein the 11βHSD1 inhibitory effect is to treat type 2 diabetes.

14. A process for preparing a compound according to claim 1, which process comprises any one of processes a) or b):

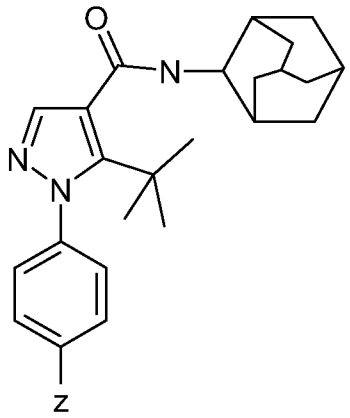
a) hydrolysis of an ester of formula (2):



(2)

wherein R^1 is an alkyl or aryl group; or

b) converting Z in a compound of the formula (3):



(3)

into a carboxy group, wherein Z is an functional group capable of conversion into a carboxylic acid;

and thereafter if necessary or desirable forming a pharmaceutically-acceptable salt thereof.