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(54) **PHARMACEUTICAL FORMULATION FOR ADMINISTRATION BY INHALATION COMPRISING AN ANDROSTANE DERIVATIVE AND A BETA-2-ADRENORECEPTOR FOR THE TREATMENT OF INFLAMMATORY AND ALLERGIC CONDITIONS**

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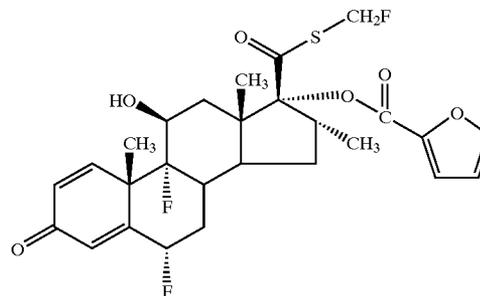
A61K 9/14

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(57) **ABSTRACT**

A pharmaceutical formulation for administration by inhalation comprising a compound of formula (I),

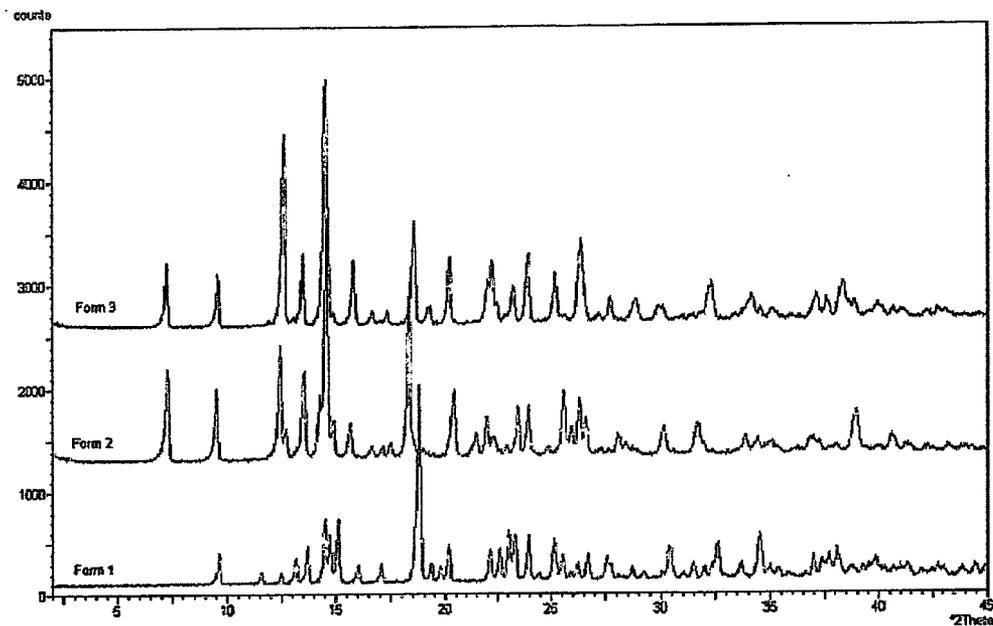
(I)



or a solvate thereof, together with a long-acting  $\beta_2$ -adreno-receptor agonist which formulation has a therapeutically useful effect in the treatment of inflammatory disorders of the respiratory tract over a period of 24 hours or more.

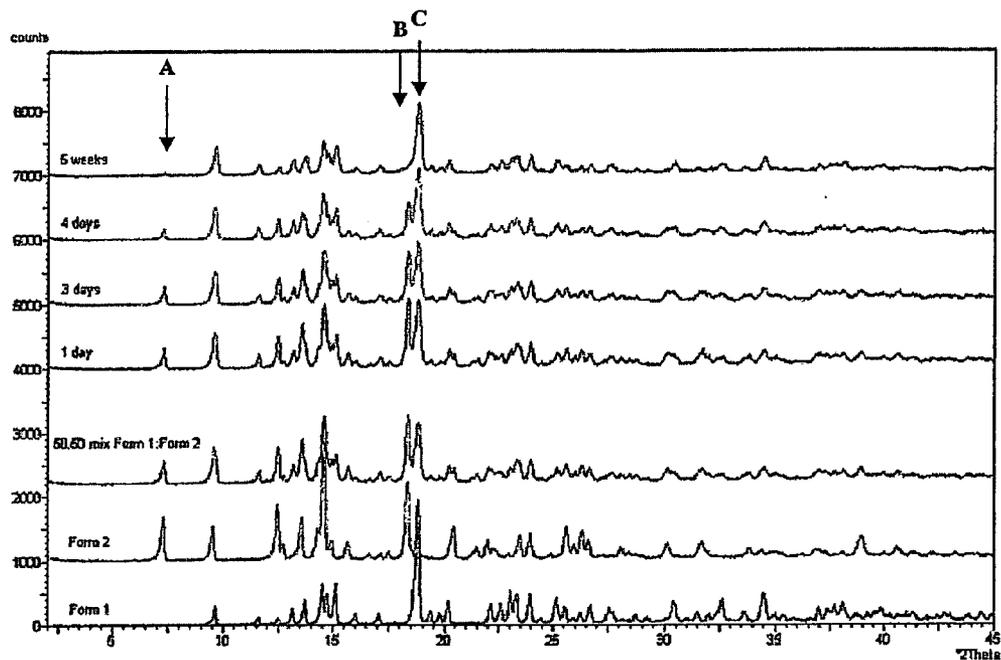
**Figure 1**

**Overlay of XRPD Profiles of 3 polymorphs of Unsolvated Compound of Formula (I)**



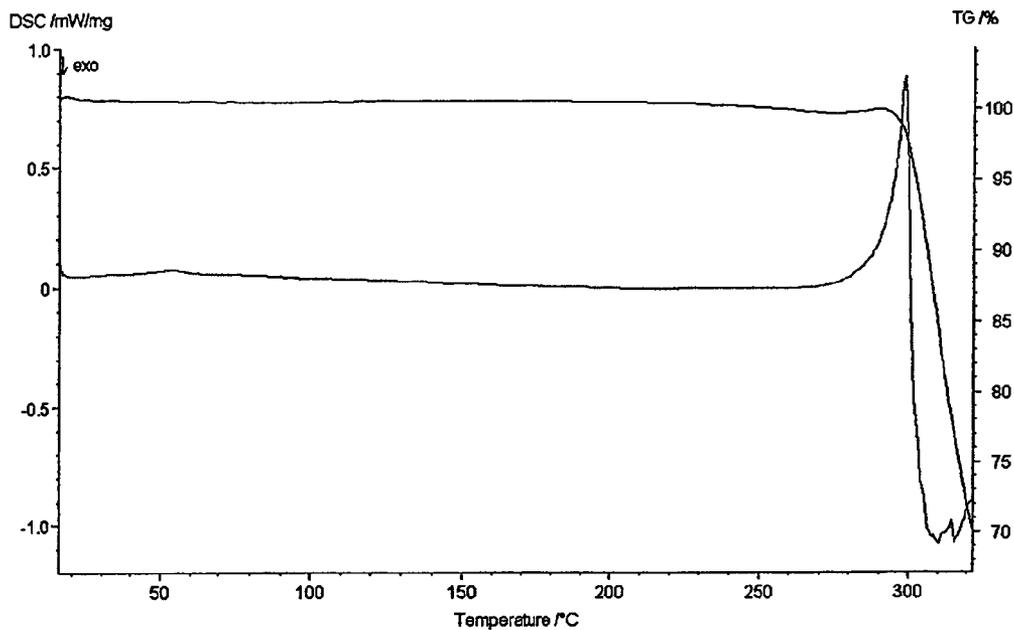
**Figure 2**

**Overlay of XRPD Profiles of Form 1, Form 2 and a 50:50 mixture of Form 1 and Form 2 Polymorphs of Unsolvated Compound of Formula (I), together with the time-dependence of the profile of the mixture**



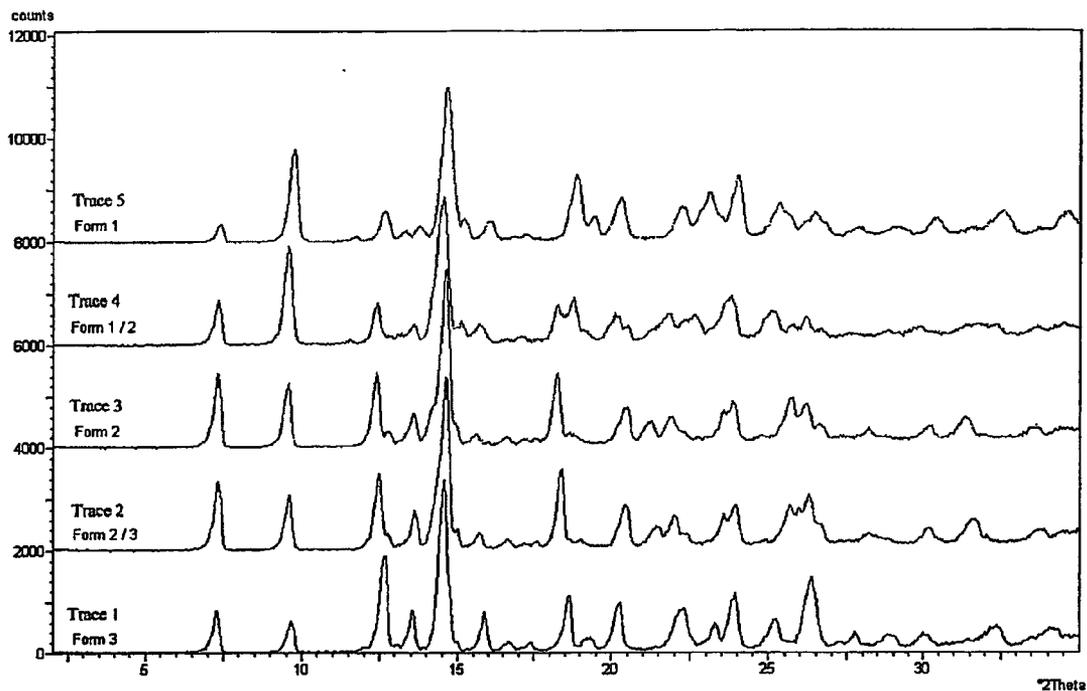
**Figure 3**

**DSC and TGA Profiles of Form 1 polymorph of Unsolvated Compound of Formula (I)**



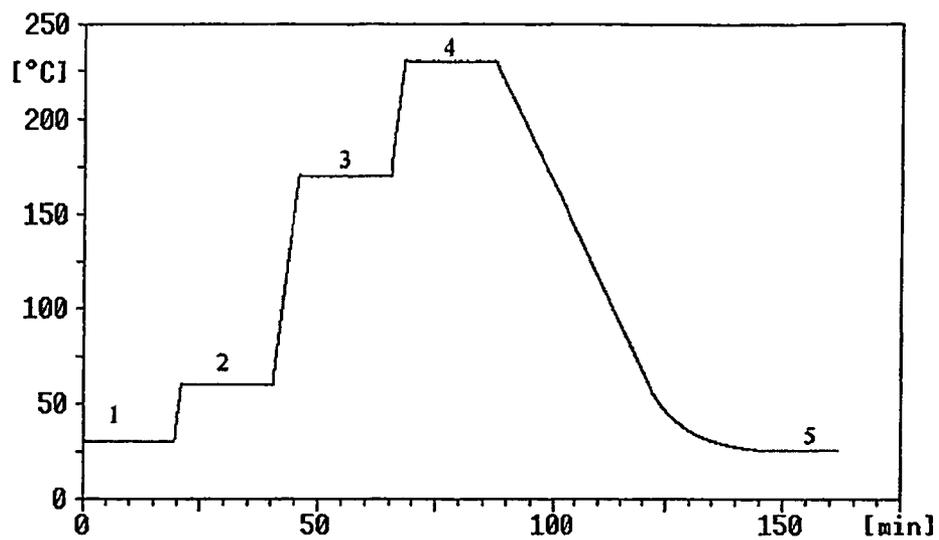
**Figure 4**

**Temperature dependence of the XRPD profile of Compound of formula (I) Unsolvated Form 3 (temperature and time profile is shown in Figure 5)**

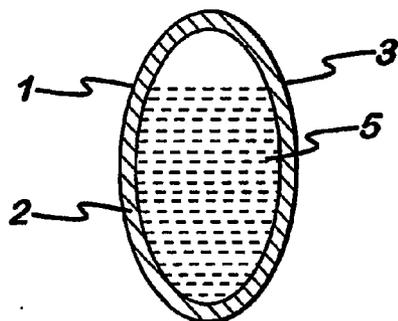


**Figure 5**

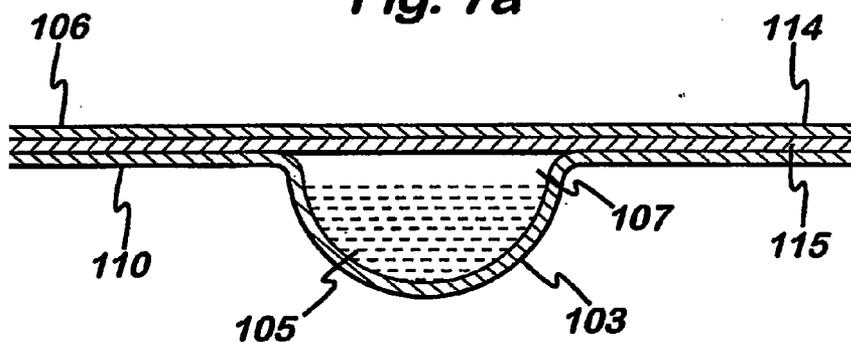
**Temperature and time profile for the XRPD experiments shown in Figure 4**



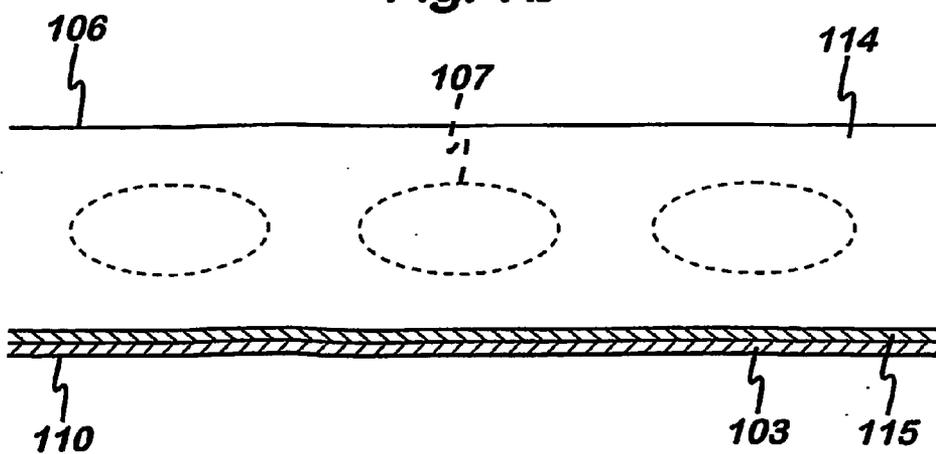
**Fig. 6**



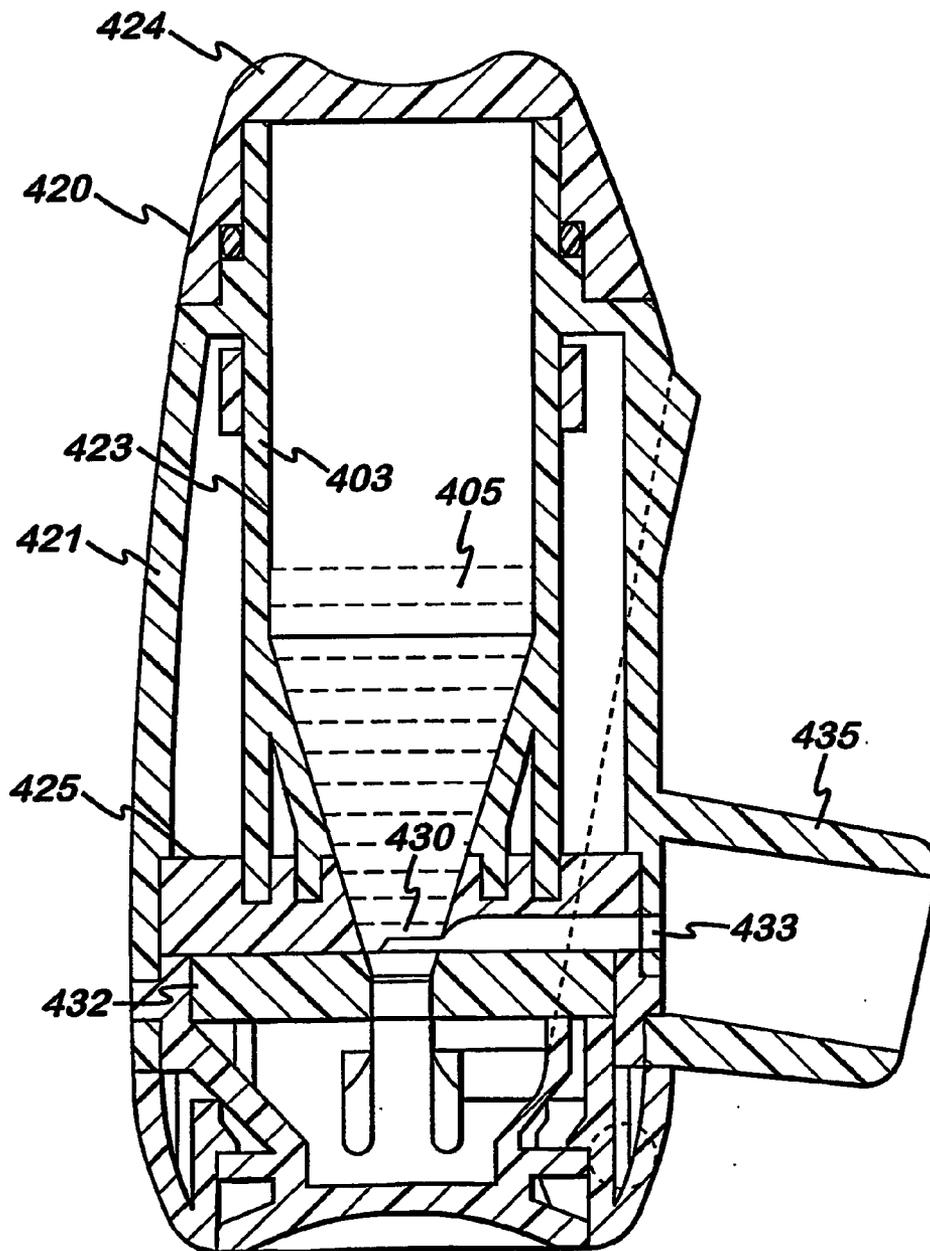
**Fig. 7a**



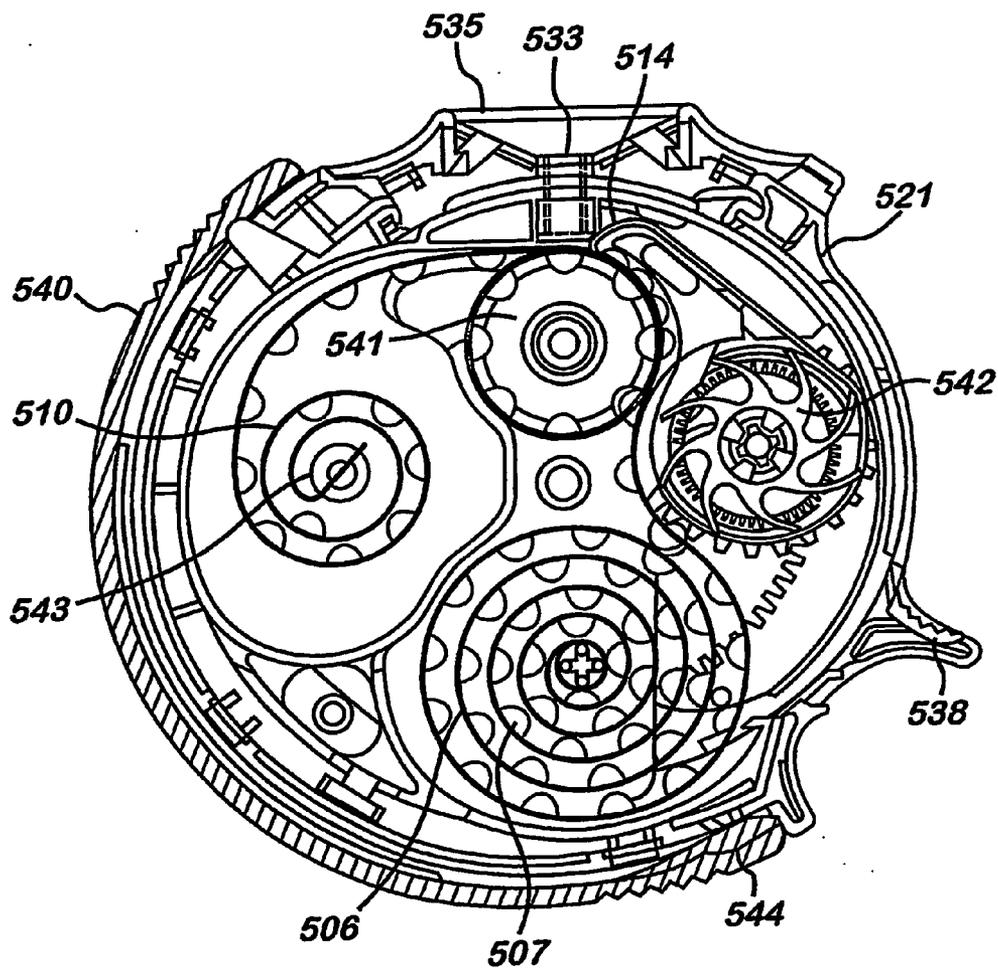
**Fig. 7b**



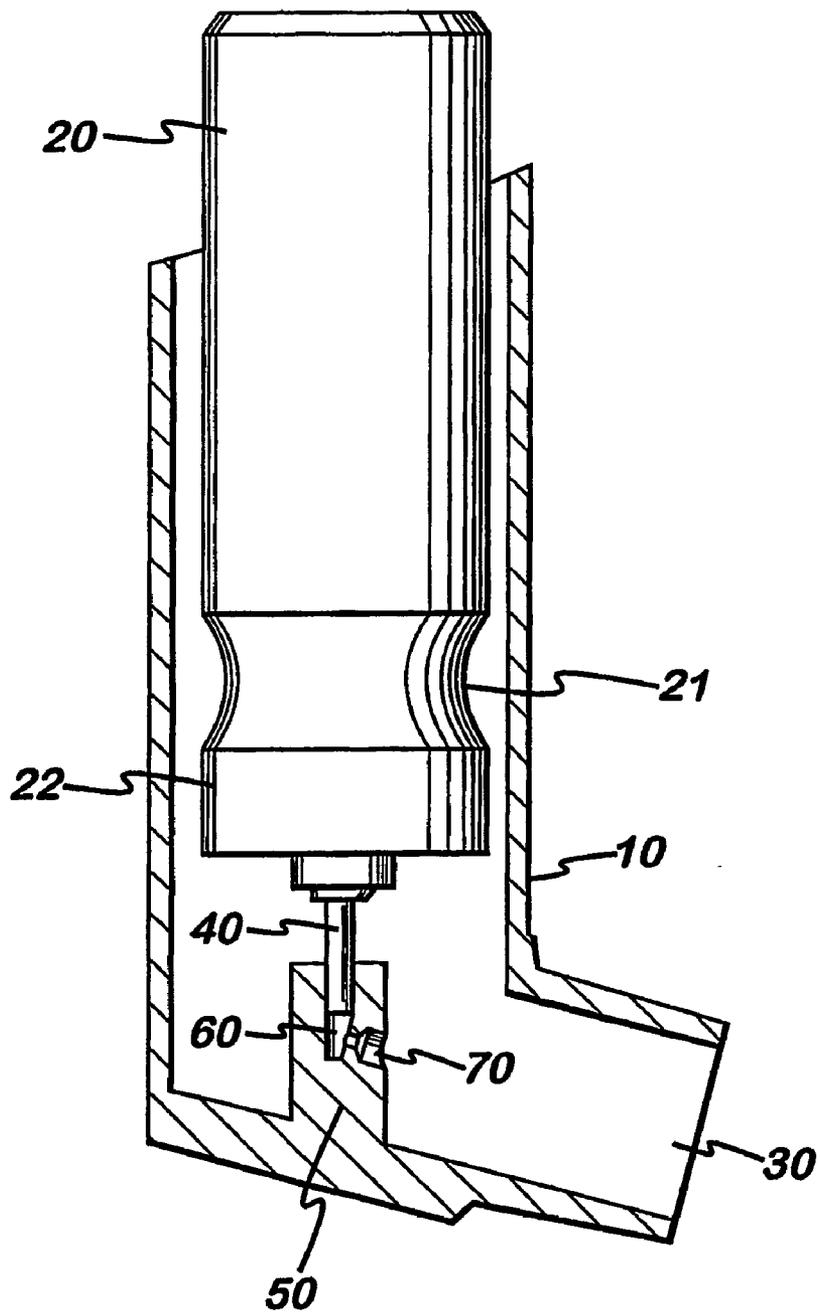
**Fig. 8**



**Fig. 9**



**Fig. 10**



**PHARMACEUTICAL FORMULATION FOR  
ADMINISTRATION BY INHALATION  
COMPRISING AN ANDROSTANE DERIVATIVE  
AND A BETA-2-ADRENORECEPTOR FOR THE  
TREATMENT OF INFLAMMATORY AND  
ALLERGIC CONDITIONS**

[0001] This application is a Continuation-in-part of U.S. patent application Ser. No. 09/958,050 filed on 2 Oct. 2001, which is based upon International Patent Application No. PCT/GB01.03495 filed 3 Aug. 2001, which claims priority to United Kingdom Patent Application No. GB 0019172.6 filed 5 Aug. 2000.

[0002] The present invention relates to a novel formulations of anti-inflammatory and anti-allergic formulations of the androstane series and  $\beta_2$ -adrenoreceptor agonists and to processes for its preparation. The present invention also relates to pharmaceutical formulations containing the compound and to therapeutic uses thereof, particularly for the treatment of inflammatory and allergic conditions.

[0003] Glucocorticoids which have anti-inflammatory properties are known and are widely used for the treatment of inflammatory disorders or diseases such as asthma and rhinitis. For example, U.S. Pat. No. 4,335,121 discloses  $6\alpha$ ,  $9\alpha$ -Difluoro- $17\alpha$ -(1-oxopropoxy)- $11\beta$ -hydroxy- $16\alpha$ -methyl-3-oxo-androsta- $1,4$ -diene- $17\beta$ -carbothioic acid S-fluoromethyl ester (known by the generic name of fluticasone propionate) and derivatives thereof. The use of glucocorticoids generally, and especially in children, has been limited in some quarters by concerns over potential side effects. The side effects that are feared with glucocorticoids include suppression of the Hypothalamic-Pituitary-Adrenal (HPA) axis, effects on bone growth in children and on bone density in the elderly, ocular complications (cataract formation and glaucoma) and skin atrophy. Certain glucocorticoid compounds also have complex paths of metabolism wherein the production of active metabolites may make the pharmacodynamics and pharmacokinetics of such compounds difficult to understand. Whilst the modern steroids are very much safer than those originally introduced, it remains an object of research to produce new molecules which have excellent anti-inflammatory properties, with predictable pharmacokinetic and pharmacodynamic properties, with an attractive side effect profile, and with a convenient treatment regime.

[0004] In our application PCT.GB.01.03495 we have identified a novel glucocorticoid compound which substantially meets these objectives.

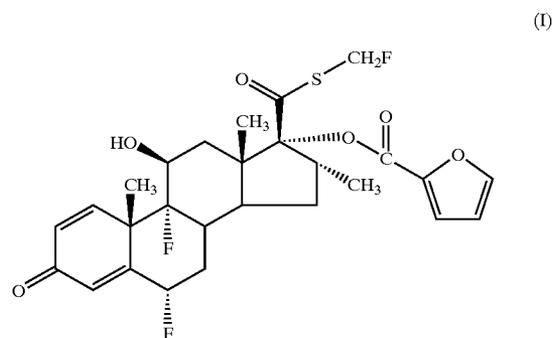
[0005] Current combination products comprising glucocorticoids and  $\beta_2$ -adrenoreceptor receptor agonists are normally administered on a twice daily regime.

[0006] It is considered that once-per-day dosing is significantly more convenient to patients than a twice-per-day

dosing regime, which is likely to lead to greater patient compliance and hence better disease control and a product providing such a dosing regime has been sought.

[0007] It is an objective of the present invention to provide safe and effective once-per-day combination formulation.

[0008] According to a first aspect of the invention, there is provided a pharmaceutical formulation for administration by inhalation comprising a compound of formula (I):



[0009] or a solvate thereof, together with a long-acting  $\beta_2$ -adrenoreceptor agonist which formulation has a therapeutically useful effect in the treatment of inflammatory disorders of the respiratory tract over a period of 24 hours or more.

[0010] The chemical name of the compound of formula (I) is  $6\alpha$ , $9\alpha$ -Difluoro- $17\alpha$ -[(2-furan-2-ylcarbonyloxy)oxy]- $11\beta$ -hydroxy- $16\alpha$ -methyl-3-oxo-androsta- $1,4$ -diene- $17\beta$ -carbothioic acid S-fluoromethyl ester.

[0011] References hereinafter to the compounds of formula (I) include both the compound of formula (I) and solvates thereof, particularly pharmaceutically acceptable solvates.

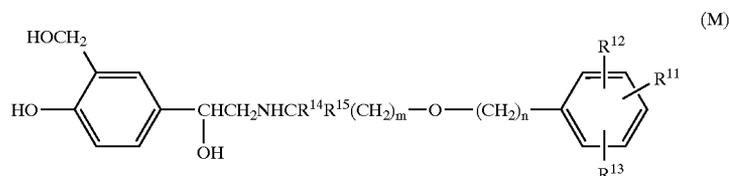
[0012] Examples of solvates include hydrates.

[0013] In some embodiments, preferred long-acting  $\beta_2$ -adrenoreceptor agonists include salmeterol or formoterol.

[0014] Particularly preferred long acting  $\beta_2$ -adrenoreceptor agonists have therapeutic effect over a 24 hour period.

[0015] In some embodiments, preferred long acting  $\beta_2$ -adrenoreceptor agonists include those described in WO 02066422, W002070490 and W002076933.

[0016] Especially preferred long-acting  $\beta_2$ -adrenoreceptor agonists include compounds of formula (M):



[0017] or a salt or solvate thereof, wherein:

[0018]  $m$  is an integer of from 2 to 8;

[0019]  $n$  is an integer of from 3 to 11,

[0020] with the proviso that  $m+n$  is 5 to 19,

[0021]  $R^{11}$  is  $—XSO_2NR^{16}R^{17}$  wherein  $X$  is  $—(CH_2)_p—$  or  $C_{2-5}$  alkenylene;

[0022]  $R^{16}$  and  $R^{17}$  are independently selected from hydrogen,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl,

[0023]  $C(O)NR^{18}R^{19}$ , phenyl, and phenyl ( $C_{1-6}$ alkyl),

[0024] or  $R^{16}$  and  $R^{17}$ , together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and  $R^{16}$  and  $R^{17}$  are each optionally substituted by one or two groups selected from halo,  $C_{1-6}$ alkyl,  $C_{1-6}$ -haloalkyl,  $C_{1-6}$ alkoxy, hydroxy-substituted  $C_{1-6}$ alkoxy,  $—CO_2R^{18}$ ,  $—SO_2NR^{18}R^{19}$ ,  $—CONR^{18}R^{19}$ ,  $—NR^{18}C(O)R^{19}$ , or a 5-, 6- or 7-membered heterocyclic ring;

[0025]  $R^{18}$  and  $R^{19}$  are independently selected from hydrogen,  $C_{1-6}$ alkyl,

[0026]  $C_{3-6}$ cycloalkyl, phenyl, and phenyl ( $C_{1-4}$ alkyl); and

[0027]  $p$  is an integer of from 0 to 6, preferably from 0 to 4;

[0028]  $R^{12}$  and  $R^{13}$  are independently selected from hydrogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, halo, phenyl, and  $C_{1-6}$ haloalkyl; and

[0029]  $R^{14}$  and  $R^{15}$  are independently selected from hydrogen and  $C_{1-4}$ alkyl with the proviso that the total number of carbon atoms in  $R^{14}$  and  $R^{15}$  is not more than 4.

[0030] The compound of formula (I) has potentially beneficial anti-inflammatory or anti-allergic effects, particularly upon topical administration, demonstrated by, for example, its ability to bind to the glucocorticoid receptor and to illicit a response via that receptor, with long acting effect. Hence, the compound of formula (I) is useful in the treatment of inflammatory and/or allergic disorders, especially in once-per-day therapy.

[0031] Preferably in the pharmaceutical formulation of the invention the compound of formula (I) or a solvate thereof and the long-acting  $\beta_2$ -adrenoreceptor agonist are both present in particulate form.

[0032] The pharmaceutical formulation of the invention may comprise one or more excipients.

[0033] By the term “excipient”, as used herein, it is meant to mean substantially inert materials that are nontoxic and do not interact with other components of a composition in a deleterious manner including, but not limited to, pharmaceutical grades of: carbohydrates, organic and inorganic salts, polymers, amino acids, phospholipids, wetting agents, emulsifiers, surfactants, poloxamers, pluronics, and ion

exchange resins, and combinations thereof, a non-exhaustive list of examples of which are provided below:

[0034] Carbohydrates, including: monosaccharides, such as, but not limited to, fructose; disaccharides, such as, but not limited to, lactose, and combinations and derivatives thereof; polysaccharides, such as, but not limited to, cellulose and combinations and derivatives thereof; oligosaccharides, such as, but not limited to, dextrans, and combinations and derivatives thereof; polyols, such as but not limited to sorbitol, and combinations and derivatives thereof;

[0035] Organic and inorganic salts, including but not limited to sodium or calcium phosphates, magnesium stearate, and combinations and derivatives thereof;

[0036] Polymers, including: natural biodegradable protein polymers including, but not limited to, gelatin and combinations and derivatives thereof; Natural biodegradable polysaccharide polymers including, but not limited to, chitin and starch, crosslinked starch, and combinations and derivatives thereof; Semisynthetic biodegradable polymers including, but not limited to, derivatives of chitosan; Synthetic biodegradable polymers including but not limited to polyethylene glycols (PEG), polylactic acid (PLA), synthetic polymers including but not limited to polyvinyl alcohol and combinations and derivatives thereof;

[0037] Amino acids including but not limited to including non-polar amino acids, such as leucine and combinations and derivatives thereof;

[0038] Phospholipids, including lecithins and combinations and derivatives thereof;

[0039] Wetting agents/Surfactants/Emulsifiers, including, but not limited to gum acacia, cholesterol, fatty acids including, combinations and derivatives thereof;

[0040] Poloxamers/Pluronic: including but not limited to poloxamer 188, Pluronic® F-108, and combinations and derivations thereof;

[0041] Ion exchange resins: including but not limited to amberlite IR120 and combinations and derivatives thereof;

[0042] and combinations of the noted excipients.

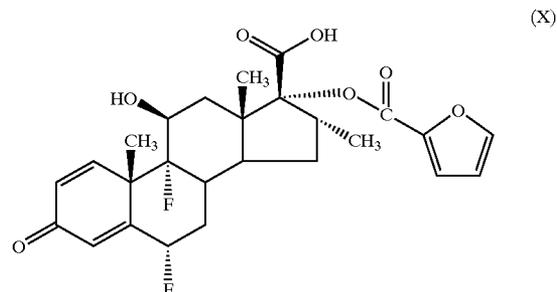
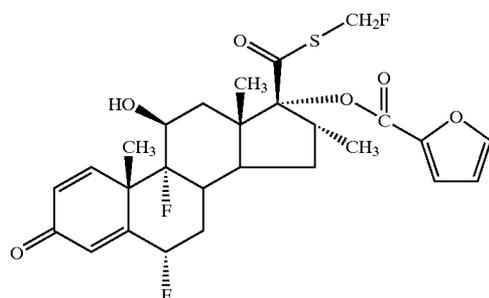
[0043] The pharmaceutical formulation of the invention preferably further comprises a particulate carrier, preferably lactose.

[0044] The pharmaceutical formulation of the invention preferably further comprises a liquified propellant gas.

[0045] According to a second aspect or the present invention there is provided a method of treatment of an inflammatory disorder of the respiratory tract once-per-day which comprises administration of a pharmaceutical formulation according to the first aspect of the invention.

[0046] According to a third aspect of the present invention there is provided an inhaler containing a plurality of doses of a pharmaceutical formulation comprising a compound of formula (I)

>1000 fold less active than the parent compound in in vitro functional glucocorticoid assays.



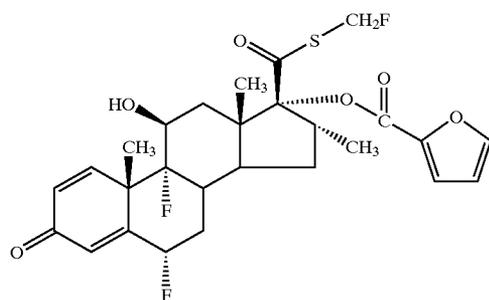
[0047] or a solvate thereof, together with a long-acting  $\beta_2$ -adrenoreceptor agonist, which formulation has a therapeutically useful effect in the treatment of inflammatory disorders of the respiratory tract over a period of 24 hours or more, and which doses are suitable for once-per-day administration of the formulation by inhalation.

[0048] Preferably the compound of formula (I) or a solvate thereof and the long-acting 2-adrenoreceptor agonist are both present in particulate form in the inhaler.

[0049] In the inhaler of the invention preferably the formulation further comprises a particulate carrier, especially lactose.

[0050] In the inhaler of the present invention, the formulations preferably further comprises a liquefied propellant gas.

[0051] Preferably the inhaler contains a plurality of doses of the pharmaceutical formulation of the invention comprising a particulate compound of formula (I)



[0052] In the inhaler of the present invention the inflammatory disorder of the respiratory tract is preferably asthma.

[0053] In the inhaler according to the present invention the long-acting  $\beta_2$ -adrenoreceptor agonist is a compound of the formula (M) as described above.

[0054] Compound (I) undergoes highly efficient hepatic metabolism to yield the 17- $\beta$  carboxylic acid (X) as the sole major metabolite in rat and human in vitro systems. This metabolite has been synthesised and demonstrated to be

[0055] This efficient hepatic metabolism is reflected by in vivo data in the rat, which have demonstrated plasma clearance at a rate approaching hepatic blood flow and an oral bioavailability of <1%, consistent with extensive first-pass metabolism.

[0056] In vitro metabolism studies in human hepatocytes have demonstrated that compound (I) is metabolised in an identical manner to fluticasone propionate but that conversion of (I) to the inactive acid metabolite occurs approximately 5-fold more rapidly than with fluticasone propionate. This very efficient hepatic inactivation would be expected to minimise systemic exposure in man leading to an improved safety profile.

[0057] Inhaled steroids are also absorbed through the lung and this route of absorption makes a significant contribution to systemic exposure. Reduced lung absorption could therefore provide an improved safety profile. Studies with compound of formula (I) have shown significantly lower systemic exposure to compound of formula (I) than with fluticasone propionate after dry powder delivery to the lungs of anaesthetised pigs.

[0058] We have also surprisingly found that the compound of Formula (I) shows a significantly longer mean absorption time (MAT) than fluticasone propionate, in man. Measurements have shown that the compound of Formula (I) has a mean absorption time of an average of 12 hours while fluticasone propionate has a MAT of an average of 2.1 hours. Mathematical deconvolution of the plasma concentration time data shows that the time taken for 90% of lung dose to be absorbed is on average, 21 hours for compounds of Formula (I) compared with 11 hours for fluticasone propionate. It has been shown that oral bioavailability of the compound of Formula (I) is very low, and therefore systemic exposure is predominantly the result of absorption from the lung. This would suggest that the compound of Formula (I) has a significantly longer residence time in the lung than fluticasone propionate.

[0059] A longer residence time in the lung may lead to a longer duration of action and the lower daily systemic exposure may lead to an improved safety profile which, it is believed, allows the compound of formula (I) to demonstrate the desired anti-inflammatory effects when administered once-per day. Once-per-day dosing is considered to be significantly more convenient to patients than the twice-per day dosing regime that is normally employed for fluticasone propionate.

[0060] In vitro human lung tissue affinity experiments indicate significantly higher affinity of the compound of formula (I) for human lung tissue preparations than does fluticasone propionate.

[0061] This is supported also by cell transport and accumulation studies using human bronchial epithelial cells. These studies show reduced flux across the cell layer for compound of formula (I) compared with fluticasone propionate. The studies also show greater accumulation of the compound of formula (I) within the cell layer compared with fluticasone propionate.

[0062] Examples of disease states in which the formulation of the invention has utility include inflammatory conditions of the nose, throat or lungs such as asthma (including allergen-induced asthmatic reactions), rhinitis (including hayfever), chronic obstructive pulmonary disease (COPD), interstitial lung disease, and fibrosis.

[0063] The formulation of the present invention is expected to be most useful in the treatment of inflammatory disorders of the respiratory tract eg asthma and COPD, particularly asthma.

[0064] It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

[0065] As mentioned above, the formulation of the present invention is useful in human or veterinary medicine, in particular as an anti-inflammatory and anti-allergic agent.

[0066] There is thus provided as a further aspect of the invention the formulation of the present invention for use in human or veterinary medicine, particularly in the treatment of patients with inflammatory and/or allergic conditions, especially for treatment once-per-day.

[0067] According to another aspect of the invention, there is provided the use of the formulation of the present invention for the manufacture of a medicament for the treatment of patients with inflammatory and/or allergic conditions, especially for treatment once-per-day.

[0068] In a further or alternative aspect, there is provided a method for the treatment of a human or animal subject with an inflammatory and/or allergic condition, which method comprises administering to said human or animal subject an effective amount of the formulation of the present invention especially for administration once-per-day.

[0069] The formulation of the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising the compound of formula (I) or a physiologically acceptable solvate thereof together, if desirable, in admixture with one or more physiologically acceptable diluents or carriers.

[0070] Further, there is provided a process for the preparation of such pharmaceutical compositions which comprises mixing the ingredients.

[0071] The compounds according to the invention may for example be formulated for insufflation or inhalation.

[0072] Advantageously compositions for topical administration to the lung include dry powder compositions and spray compositions.

[0073] Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in pre-metered capsules and cartridges for use in an inhaler or insufflator of, for example, gelatine. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a formulation according to the first aspect of the invention preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

[0074] The dry powder formulation may be presented as blends or or composite particles, or as blends of composite particles. The blended formulations generally contain micronized separate particles of active agent(s) and a suitable powder base such as lactose or starch. Use of lactose is preferred. The powder base acts as a diluent allowing the actives to be effectively metered, as well as providing and improving the flow properties of the dry powder composition. Blends may also contain additional components, such as flow enhancers, chemical or physical stabilizers, diluents, and flavor masking agents, as will be appreciated by those of ordinary skill in the art. Each capsule or cartridge may generally contain between 20  $\mu$ g-10 mg of the compound of formula (I) and a long acting  $\beta_2$ -adrenoreceptor agonist.

[0075] Composite particles may include, in any given particle within a powder composition, one or more active agents, and optionally, one or more further excipients. Such excipients may be suitable for sustaining or controlling the release of the active agents from the powder particle containing such active agent (for example, such as through using of hydrophobic or hydrophilic coating or matrixing agents in the dry powder particles). Additionally, or alternatively, the excipients may increase the physical and/or chemical stability or the medicament particles, and/or increase powder flow properties of the powder composition, thus making the dry powder more dispersible. Such excipients may form a matrix with the active or active agents, or may coat or be coated by the active or active agents. Additionally, and alternatively, the composite particles may be formulated with particles having a different composition, thus forming a blend of particles presented as a dry powder composition.

[0076] Alternatively, the compound of the invention may be presented without excipients.

[0077] Such dry powders may be formed by micronization, bead milling, and known particle formulation or co-

precipitation techniques (such as single or double emulsion techniques) spray drying, spray coating, sonocrystallisation, and the like.

[0078] In addition to these dry powder compositions, the compounds of the present invention may be presented as spray composition.

[0079] Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. The aerosol composition may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. One example formulation is excipient free and consists essentially of (eg consists of) compound of formula (I) (preferably in unsolvated form eg as Form 1) (optionally together with a further active ingredient) and a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane and mixture thereof. Another example formulation comprises particulate compound of formula (I), a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane and mixture thereof and a suspending agent which is soluble in the propellant eg an oligolactic acid or derivative thereof as described in WO94/21229. The preferred propellant is 1,1,1,2-tetrafluoroethane. As noted elsewhere in this specification, compound of formula (I) does not appear to form a solvate with 1,1,1,2-tetrafluoroethane. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

[0080] Pressurised aerosol formulations preferably do not comprise particulate medicament, a propellant and a stabiliser comprising a water addition (i.e. water added in addition to nascent formulation water). Pressurised aerosol formulations also preferably do not comprise particulate medicament, a propellant and a stabiliser comprising an amino acid, a derivative thereof or a mixture thereof.

[0081] Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10  $\mu\text{m}$ , preferably 2-5  $\mu\text{m}$ . Particles having a size above 20  $\mu\text{m}$  are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of compound of formula (I) (and any further therapeutically active ingredient) as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline, prepared for example by a process which comprises mixing in a continuous flow cell in the presence of ultrasonic radiation a flowing solution of compound of formula (I) as medicament in a liquid solvent with a flowing liquid antisolvent for said medicament (eg as described in International Patent

Application PCT/GB99/04368) or else by a process which comprises admitting a stream of solution of the substance in a liquid solvent and a stream of liquid antisolvent for said substance tangentially into a cylindrical mixing chamber having an axial outlet port such that said streams are thereby intimately mixed through formation of a vortex and precipitation of crystalline particles of the substance is thereby caused (eg as described in International Patent Application PCT/GB00/04327). When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90  $\mu\text{m}$  and not less than 15% will have a MMD of less than 15  $\mu\text{m}$ .

[0082] Formulations for administration typically to the nose (eg for the treatment of rhinitis) include pressurised aerosol formulations and aqueous formulations administered to the nose by pressurised pump. Formulations which are non-pressurised and adapted to be administered topically to the nasal cavity are of particular interest. The formulation preferably contains water as the diluent or carrier for this purpose.

[0083] Aqueous formulations for administration to the lung or nose may be provided with conventional excipients such as buffering agents, tonicity modifying agents and the like. Aqueous formulations may also be administered to the nose by nebulisation.

[0084] If appropriate, the formulations of the invention may be buffered by the addition of suitable buffering agents.

[0085] The proportion of the active compound of formula (I) in the formulation according to the invention depends on the precise type of formulation to be prepared but will generally be within the range of from 0.001 to 10% by weight. Generally, however for most types of preparations advantageously the proportion used will be within the range of from 0.005 to 1% and preferably 0.01 to 0.5%. However, in powders for inhalation or insulation the proportion used will usually be within the range of from 0.1 to 5%.

[0086] Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains 1  $\mu\text{g}$ -2000  $\mu\text{g}$  eg 20  $\mu\text{g}$ -2000  $\mu\text{g}$ , preferably about 20  $\mu\text{g}$ -500  $\mu\text{g}$  of a compound of formula (I) optionally in combination with another therapeutically active ingredient. Administration may be once daily or several times daily, for example 2, 3, 4 or 8 times, giving for example 1, 2 or 3 doses each time. Preferably the compound of formula (I) is delivered once or twice daily, more preferably once-per-day. The overall daily dose with an aerosol will typically be within the range 10  $\mu\text{g}$ -10 mg eg 100  $\mu\text{g}$ -10 mg preferably, 200  $\mu\text{g}$ -2000  $\mu\text{g}$ .

[0087] The formulations are preferably arranged so that each metered dose or puff contains 0.5  $\mu\text{g}$  to 1000  $\mu\text{g}$ , preferably about 5  $\mu\text{g}$  to 500  $\mu\text{g}$  of long-acting  $\beta_2$ -adrenoceptor agonist.

[0088] The ratio of the long-acting  $\beta_2$ -adrenoceptor agonist to the compound of formula (I) is preferably within the range 4:1 to 1:20.

[0089] Each metered dose or actuation of the inhaler preferably will contain from 10  $\mu\text{g}$  to 100  $\mu\text{g}$  of the long-

acting  $\beta_2$ -adrenoreceptor agonist and from 25  $\mu\text{g}$  to 500  $\mu\text{g}$  of a compound of formula (I).

[0090] Typically, each metered dose will contain about 25  $\mu\text{g}$  of long acting  $\beta_2$ -adrenoreceptor agonist and about 250  $\mu\text{g}$  of a compound of formula (I) per 50  $\mu\text{l}$  actuation.

[0091] Since the compound of formula (I) is long-acting, the composition comprising the compound of formula (I) and the long-acting  $\beta_2$ -adrenoreceptor agonist (M) will be delivered once-per-day and the dose of each will be selected so that the composition has a therapeutic effect in the treatment of respiratory disorders effect (eg in the treatment of asthma or COPD, particularly asthma) over 24 hours or more.

[0092] The pharmaceutical formulation according to the invention may also be used in combination with another therapeutically active agent, for example an anti-histamine or an anti-allergic. Anti-histamines include methapyrilene or loratadine.

[0093] Other suitable combinations include, for example, other anti-inflammatory agents eg. NSAIDs (eg. PDE4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists) or anti-infective agents (eg. antibiotics, antivirals).

[0094] The formulation according to the invention in combination with another therapeutically active ingredient as described above may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising the compound of formula (I) or a physiologically acceptable solvate thereof in combination with another therapeutically active ingredient together, if desirable, in admixture with one or more physiologically acceptable diluents or carriers. The preferred route of administration for inflammatory disorders of the respiratory tract will generally be administration by inhalation.

[0095] Further, there is provided a process for the preparation of such pharmaceutical compositions which comprises mixing the ingredients.

[0096] The individual compounds of such combinations may be administered either sequentially in separate pharmaceutical compositions as well as simultaneously in combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

[0097] Surprisingly, the compound of formula (I) has demonstrated a significant propensity to form solvates with commonly used organic solvents. Such solvates are essentially stoichiometric eg the ratio of compound of formula (I) to solvent is close to 1:1 eg according to Applicant's analysis has been determined to be in the range 0.95:1 to 1.05:1. For example, we have prepared solvates with solvents such as acetone, dimethylformamide (DMF), dimethylacetamide (DMAc), tetrahydrofuran (THF), N-methyl-2-pyrrolidone, isopropanol and methylethylketone. The solvation of compound of formula (I) is not predictable however since we have found that even though it does form a solvate with isopropanol it does not appear to form a solvate with ethanol or methanol. Furthermore it does not appear to form a solvate with 1,1,1,2-tetrafluoroethane, ethylacetate, methy-

lacetate, toluene, methylisobutylketone (MIBK) or water either. However due to the toxicity of many organic solvents it has been necessary to develop special final stage processing conditions (discussed later) in order to permit the compound of formula (I) to be produced in unsolvated form. Thus according to another aspect of the invention there is provided a compound of formula (I) in unsolvated form.

[0098] Surprisingly we have also discovered that the compound of formula (I) in unsolvated form may exist in a number of polymorphic forms. Specifically we have identified polymorphic forms which may be distinguished by means of X-Ray Powder

[0099] Diffraction (XRPD) which we have named as Form 1, Form 2 and Form 3. Form 3 appears to be an unstable minor polymorphic modification of Form 2.

[0100] Broadly speaking the Forms are characterised in their XRPD profiles as follows:

[0101] Form 1: Peak at around 18.9 degrees 2Theta

[0102] Form 2: Peaks at around 18.4 and 21.5 degrees 2Theta.

[0103] Form 3: Peaks at around 18.6 and 19.2 degrees 2Theta.

[0104] Within the range 21-23 degrees 2Theta Form 3 shows a single peak whereas Form 2 shows a pair of peaks. A peak at 7 degrees 2Theta is present in all cases however it is present at much higher intensity in the case of Forms 2 and 3 than is the case for Form 1.

[0105] The XRPD patterns of the polymorphs are shown overlaid in FIG. 1. The conversion of Form 2 to Form 1 with time in an aqueous slurry at ambient temperature is shown in FIG. 2. In the conversion of Form 2 to Form 1 the loss of a peak characteristic of Form 2 (labelled B) at around 18.4 degrees 2Theta, a marked reduction in intensity in the peak at around 7 degrees 2Theta (labelled A) and the appearance of a peak characteristic of Form 1 (labelled C) at around 18.9 degrees 2Theta are particularly noticeable.

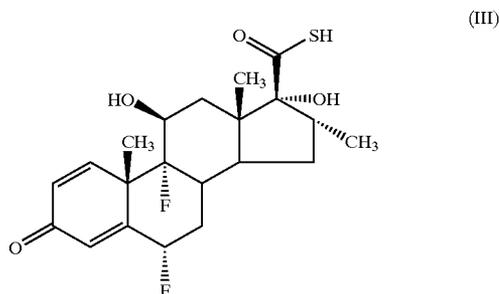
[0106] The temperature dependence of Form 3 is shown in FIG. 4. The temperature was varied according to the profile shown in FIG. 5. From FIG. 4 it can be seen that Form 3 converts first to Form 2 over the temperature range 30-170° C. and then converts to Form 1 over the temperature range 170-230° C. In the conversion of Form 3 to Form 2 the division of one peak in the range 21-23 degrees 2Theta into two peaks within the same range and the shifting leftwards of the peak at around 18.6 degrees 2Theta to around 18.4 degrees 2Theta are particularly noticeable. In the conversion of Form 2 to Form 1 similar changes to those noted in the previous paragraph may be observed.

[0107] The differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profiles of Form 1 are shown in FIG. 3. The profiles are characterised by a transition at around 280-300° C. (typically close to 298° C.) corresponding to an endothermic event in the DSC and chemical degradation in the TGA. The DSC profiles of Forms 2 and 3 were not materially different under the conditions of the experiments performed and thus DSC is not a suitable technique for distinguishing between the 3 Forms. In FIG. 3 the absence of activity in the TGA and



of formula (I) so produced in solution in ethylacetate is distilled and toluene added, then unsolvated Form 1 crystallises out.

[0127] Compounds of formula (II) may be prepared from the corresponding 17 $\alpha$ -hydroxyl derivative of formula (III):



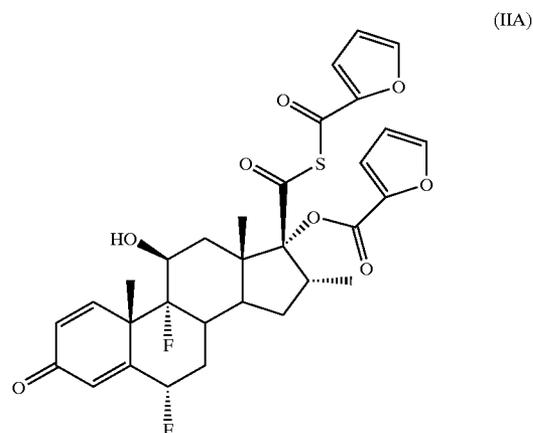
[0128] using for example, the methodology described by G. H. Phillipps et al., (1994) *Journal of Medicinal Chemistry*, 37, 3717-3729. For example the step typically comprises the addition of a reagent suitable for performing the esterification eg an activated derivative of 2-furoic acid such as an activated ester or preferably a 2-furoyl halide eg 2-furoyl chloride (employed in at least 2 times molar quantity relative to the compound of formula (III)) in the presence of an organic base eg triethylamine. The second mole of 2-furoyl chloride reacts with the thioacid moiety in the compound of formula (III) and needs to be removed eg by reaction with an amine such as diethylamine.

[0129] This method suffers disadvantages, however, in that the resultant compound of formula (II) is not readily purified of contamination with the by-product 2-furoyldiethylamide. We have therefore invented several improved processes for performing this conversion.

[0130] In a first such improved process we have discovered that by using a more polar amine such as diethanolamine, a more water soluble by-product is obtained (in this case 2-furoyldiethanolamide) which permits compound of formula (II) or a salt thereof to be produced in high purity since the by-product can efficiently be removed by water washing.

[0131] Thus according to this aspect of the invention we provide a process for preparing a compound of formula (II) which comprises:

[0132] (a) reacting a compound of formula (III) with an activated derivative of 2-furoic acid as in an amount of at least 2 moles of the activated derivative per mole of compound of formula (III) to yield a compound of formula (IIA);



[0133] and

[0134] (b) removal of the sulphur-linked 2-furoyl moiety from compound of formula (IIA) by reaction of the product of step (a) with an organic primary or secondary amine base capable of forming a water soluble 2-furoyl amide.

[0135] In two particularly convenient embodiments of this process we also provide methods for the efficient purification of the end product which comprise either

[0136] (c1) when the product of step (b) is dissolved in a substantially water immiscible organic solvent, purifying the compound of formula (II) by washing out the amide by-product from step (b) with an aqueous wash, or

[0137] (c2) when the product of step (b) is dissolved in a water miscible solvent, purifying the compound of formula (II) by treating the product of step (b) with an aqueous medium so as to precipitate out pure compound of formula (II) or a salt thereof.

[0138] In step (a) preferably the activated derivative of 2-furoic acid may be an activated ester of 2-furoic acid, but is more preferably a 2-furoyl halide, especially 2-furoyl chloride. A suitable solvent for this reaction is ethylacetate or methylacetate (preferably methylacetate) (when step (c1) may be followed) or acetone (when step (c2) may be followed). Normally an organic base eg triethylamine will be present. In step (b) preferably the organic base is diethanolamine. The base may suitably be dissolved in a solvent eg methanol. Generally steps (a) and (b) will be performed at reduced temperature eg between 0 and 5° C. In step (c1) the aqueous wash may be water, however the use of brine results in higher yields and is therefore preferred. In step (c2) the aqueous medium is for example a dilute aqueous acid such as dilute HCl.

[0139] According to a related aspect of the invention we provide an alternative process for preparing a compound of formula (II) which comprises:

[0140] (a) reacting a compound of formula (III) with an activated derivative of 2-furoic acid in an amount of at least 2 moles of activated derivative per mole of compound of formula (III) to yield a compound of formula (IIA); and

[0141] (b) removal of the sulphur-linked 2-furoyl moiety from compound of formula (IIA) by reaction of the product of step (a) with a further mole of compound of formula (III) to give two moles of compound of formula (II).

[0142] In step (a) preferably the activated derivative of 2-furoic acid may be an activated ester of 2-furoic acid, but is more preferably a 2-furoyl halide, especially 2-furoyl chloride. A suitable solvent for this step is acetone. Normally an organic base eg triethylamine will be present. In step (b) a suitable solvent is DMF or dimethylacetamide. Normally an organic base eg triethylamine will be present. Generally steps (a) and (b) will be performed at reduced temperature eg between 0 and 5° C. The product may be isolated by treatment with acid and washing with water.

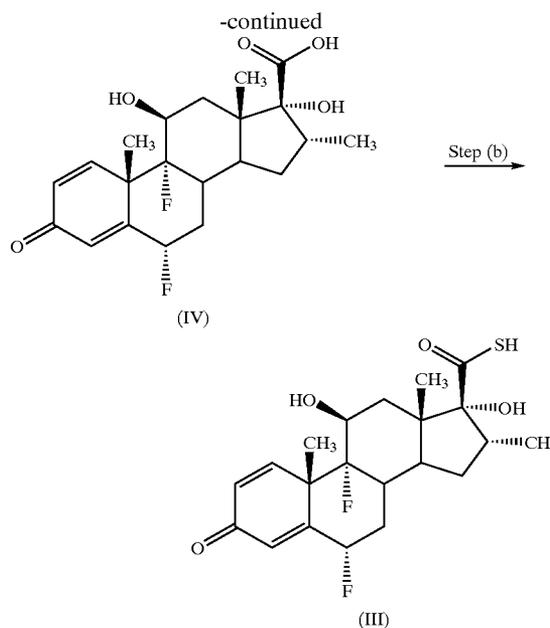
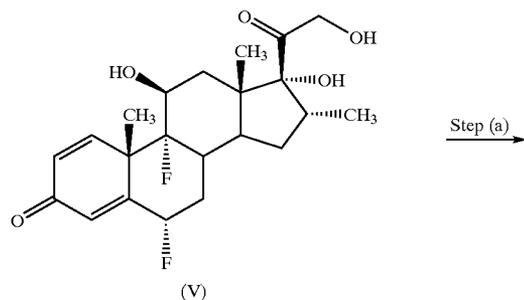
[0143] This aforementioned process is very efficient in that it does not produce any furoylamide by-product (thus affording inter alia environmental advantages) since the excess mole of furoyl moiety is taken up by reaction with a further mole of compound of formula (II) to form an additional mole of compound of formula (II).

[0144] Further general conditions for the conversion of compound of formula (III) to compound of formula (II) in the two processes just described will be well known to persons skilled in the art.

[0145] According to a preferred set of conditions, however, we have found that the compound of formula (II) may advantageously be isolated in the form of a solid crystalline salt. The preferred salt is a salt formed with a base such as triethylamine, 2,4,6-trimethylpyridine, diisopropylethylamine or N-ethylpiperidine. Such salt forms of compound of formula (II) are more stable, more readily filtered and dried and can be isolated in higher purity than the free thioacid. The most preferred salt is the salt formed with diisopropylethylamine. The triethylamine salt is also of interest.

[0146] Compounds of formula (III) may be prepared in accordance with procedures described in GB 208877B.

[0147] Compounds of formula (III) may also be prepared by a process comprising the following steps:



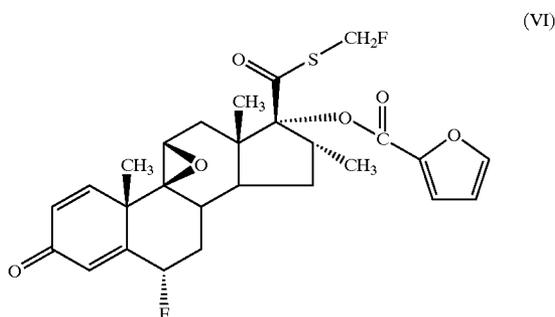
[0148] Step (a) comprises oxidation of a solution containing the compound of formula (M). Preferably, step (a) will be performed in the presence of a solvent comprising methanol, water, tetrahydrofuran, dioxan or diethylene glycol dimethylether. So as to enhance yield and throughput, preferred solvents are methanol, water or tetrahydrofuran, and more preferably are water or tetrahydrofuran, especially water and tetrahydrofuran as solvent. Dioxan and diethylene glycol dimethylether are also preferred solvents which may optionally (and preferably) be employed together with water. Preferably, the solvent will be present in an amount of between 3 and 10 vol relative to the amount of the starting material (1 wt.), more preferably between 4 and 6 vol., especially 5 vol. Preferably the oxidising agent is present in an amount of 1-9 molar equivalents relative to the amount of the starting material. For example, when a 50% w/w aqueous solution of periodic acid is employed, the oxidising agent may be present in an amount of between 1.1 and 10 wt. relative to the amount of the starting material (1 wt.), more preferably between 1.1 and 3 wt., especially 1.3 wt. Preferably, the oxidation step will comprise the use of a chemical oxidising agent. More preferably, the oxidising agent will be periodic acid or iodic acid or a salt thereof. Most preferably, the oxidising agent will be periodic acid or sodium periodate, especially periodic acid. Alternatively (or in addition), it will also be appreciated that the oxidation step may comprise any suitable oxidation reaction, eg one which utilises air and/or oxygen. When the oxidation reaction utilises air and/or oxygen, the solvent used in said reaction will preferably be methanol. Preferably, step (a) will involve incubating the reagents at room temperature or a little warmer, say around 25° C. eg for 2 hours. The compound of formula (IV) may be isolated by recrystallisation from the reaction mixture by addition of an anti-solvent. A suitable anti-solvent for compound of formula (IV) is water. Surprisingly we have discovered that it is highly desirable to control the conditions under which the compound of formula (IV) is precipitated by addition of anti-solvent eg water.

When the recrystallisation is performed using chilled water (eg water/ice mixture at a temperature of 0-5° C.) although better anti-solvent properties may be expected we have found that the crystalline product produced is very voluminous, resembles a soft gel and is very difficult to filter. Without being limited by theory we believe that this low density product contains a large amount of solvated solvent within the crystal lattice. By contrast when conditions of around 10° C. or higher are used (eg around ambient temperature) a granular product of a sand like consistency which is very easily filtered is produced. Under these conditions, crystallisation typically commences after around 1 hour and is typically completed within a few hours (eg 2 hours). Without being limited by theory we believe that this granular product contains little or no solvated solvent within the crystal lattice.

[0149] Step (b) will typically comprise the addition of a reagent suitable for converting a carboxylic acid to a carbothioic acid eg using hydrogen sulphide gas together with a suitable coupling agent eg carbonyldiimidazole (CDI) in the presence of a suitable solvent eg dimethylformamide.

[0150] An alternative process for preparing a compound of formula (II) comprises treating a compound of formula (X) with a reagent suitable for converting a carboxylic acid to a carbothioic acid eg using hydrogen sulphide gas together with a suitable coupling agent such as CDI in the presence of a suitable solvent eg DMF. Compounds of formula (X) may be prepared by methodology analogous to that described herein.

[0151] An alternative process for preparing a compound of formula (I) or a solvate thereof comprises reacting a compound of formula (VI)

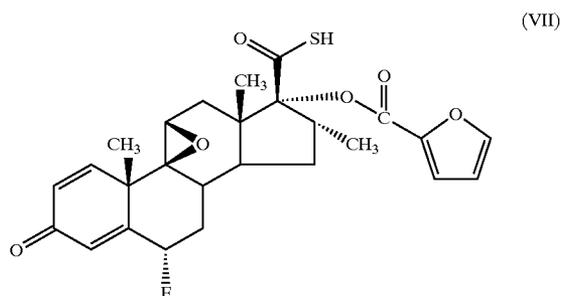


[0152] with a fluorine source.

[0153] Examples of suitable sources of fluorine include fluoride (eg sodium fluoride) or, more preferably, HF. The preferred reagent is aqueous HF. A solvent such as THF or DMF may be employed.

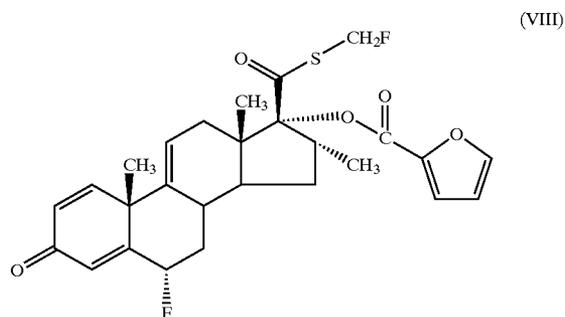
[0154] A compound of formula (VI) may be prepared by a process comprising

[0155] (a) alkylating a compound of formula (VII)



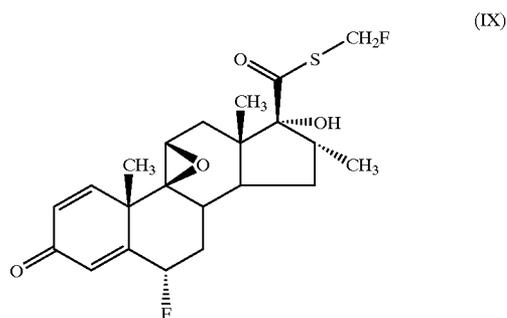
[0156] or a salt thereof;

[0157] (b) reacting a compound of formula (VII)



[0158] with an epoxide forming reagent; or

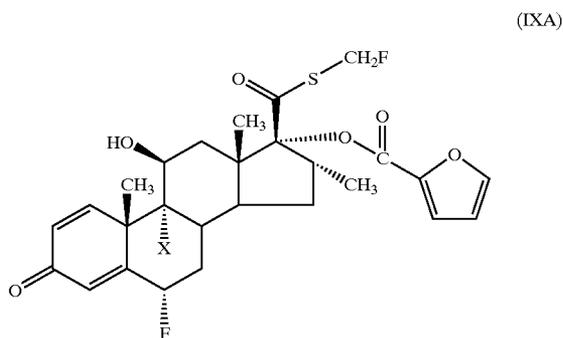
[0159] (c) esterifying a compound of formula (IX)



[0160] In process (a), analogous conditions to those described above for the conversion of a compound of formula (II) to a compound of formula (I) may be employed. Typically compound of formula (VI) will be reacted with a compound of formula FCH<sub>2</sub>L wherein L represents a leaving group (eg a halogen atom, a mesyl or tosyl group or the like) for example, an appropriate fluoromethyl halide under standard conditions. Preferably, the fluoromethyl halide reagent is bromofluoromethane.

[0161] Process (b) is preferably performed in two steps: (i) formation of a halohydrin especially a bromohydrin (eg by

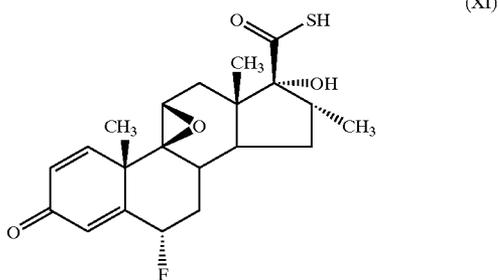
reaction with bromodan or equivalent reagent), followed by (ii) treatment with base such as sodium hydroxide so as to effect ring closure. The product of step (i) is a compound of formula (IXA) which is a novel intermediate that may be isolated, if desired:



[0162] wherein X represents halogen, especially Br.

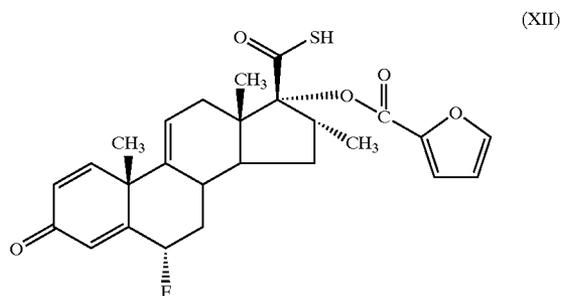
[0163] In process (c), a suitable reagent would be an activated derivative of 2-furoic acid such as an activated ester or preferably a 2-furoyl halide eg 2-furoyl chloride in the presence of an organic base eg triethylamine. This reaction may be performed at elevated temperature eg around 60° C. or else at ambient temperature in the presence of an acylation catalyst eg dimethylamino pyridine (DMAP).

[0164] Compounds of formula (VII) may be prepared by a process comprising esterification of a compound of formula (XI)



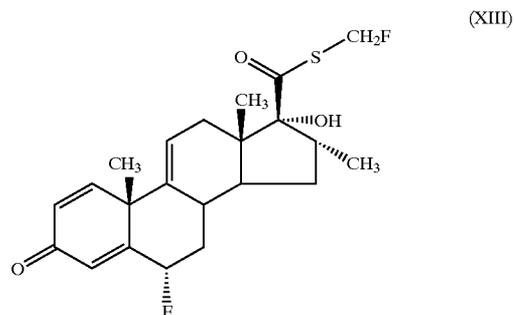
[0165] Analogous conditions to those described above for the conversion of a compound of formula (III) to a compound of formula (II) may be employed. For example, a suitable reagent would be an activated derivative of 2-furoic acid such as an activated ester or preferably a 2-furoyl halide eg 2-furoyl chloride in the presence of an organic base eg triethylamine. Compound of formula (XI) is known (J Labelled Compd Radiopharm (1997) 39(7) 567-584).

[0166] A compound of formula (VIII) may be prepared by a process comprising (a) alkylating a compound of formula (XII)



[0167] or a salt thereof, or

[0168] (b) esterifying a compound of formula (XIII)

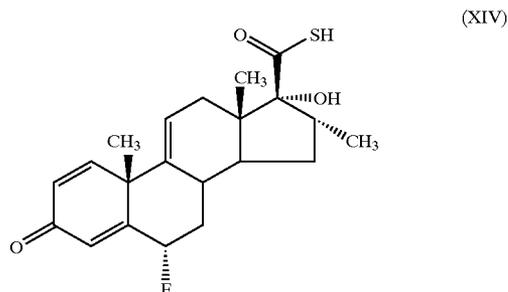


[0169] In process (a), analogous conditions to those described above for the conversion of a compound of formula (II) to a compound of formula (I) may be employed. Typically compound of formula (XII) will be reacted with a compound of formula FCH<sub>2</sub>L wherein L represents a leaving group (eg a halogen atom, a mesyl or tosyl group or the like) for example, an appropriate fluoromethyl halide under standard conditions. Preferably, the fluoromethyl halide reagent is bromofluoromethane.

[0170] In process (b), analogous conditions to those employed above for the conversion of a compound of formula (IX) to a compound of formula (VI) may be employed. For example, a suitable reagent would be an activated derivative of 2-furoic acid such as an activated ester or preferably a 2-furoyl halide eg 2-furoyl chloride in the presence of an organic base eg triethylamine.

[0171] Compounds of formula (IX) and (XIII) may be prepared by alkylating the corresponding thioacids (XI) and (XIV) (defined below) using methodology analogous to that already described (eg by reaction with a compound of formula FCH<sub>2</sub>L wherein L represents a leaving group (eg a halogen atom, a mesyl or tosyl group or the like) for example, an appropriate fluoromethyl halide under standard conditions. Preferably, the fluoromethyl halide reagent is bromofluoromethane. The thioacid (XI) is a known compound (J Labelled Compd Radiopharm (1997) 39(7) 567-584).

[0172] Compound of formula (XII) may be prepared by a process comprising esterifying a compound of formula (XIV):

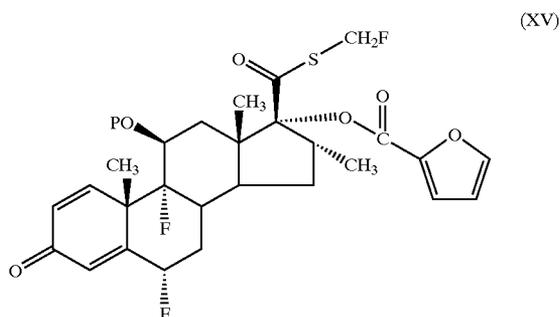


[0173] or a salt thereof.

[0174] This process may be performed using methodology analogous to that already described. For example, a suitable reagent would be an activated derivative of 2-furoic acid such as an activated ester or preferably a 2-furoyl halide eg 2-furoyl chloride in the presence of an organic base eg triethylamine.

[0175] Compounds of formula (XIV) may be prepared from the corresponding carboxylic acid eg by a process analogous to that described above for the conversion of a compound of formula (IV) to a compound of formula (III). The aforesaid corresponding carboxylic acid is known (Upjohn, WO 90/15816).

[0176] A further alternative process for preparing a compound of formula (I) or a solvate thereof comprises deprotecting or unmasking a compound of formula (I) in which the 11- $\beta$ -hydroxy group is protected or masked. A first such process comprises deprotecting a compound of formula (XV)



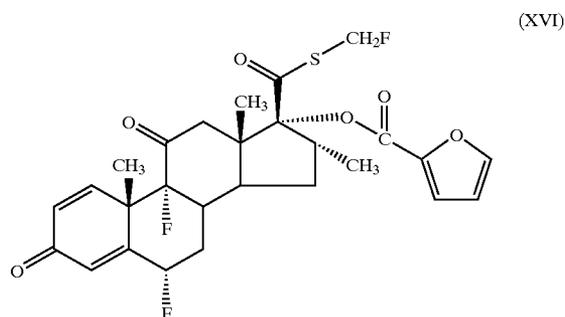
[0177] wherein P represents a hydroxy protecting group.

[0178] Examples of hydroxy protecting groups P are described in Protective Groups in Organic Chemistry Ed J F W McOmie (Plenum Press 1973) or Protective Groups in Organic Synthesis by Theodora W Green (John Wiley and Sons, 1991).

[0179] Examples of suitable hydroxy protecting groups P include groups selected from carbonate, alkyl (eg t-butyl or methoxymethyl), aralkyl (eg benzyl, p-nitrobenzyl, diphe-

nylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl (eg acetyl or benzyl) and silyl groups such as trialkylsilyl (eg t-butyltrimethylsilyl). The hydroxy protecting groups may be removed by conventional techniques. Thus, for example, carbonate may be removed by treatment with base and alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis eg by hydrolysis under acid or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis eg by hydrolysis under acidic conditions. Aralkyl groups such as benzyl or p-nitrobenzyl may be cleaved by hydrogenolysis in the presence of a Noble metal catalyst such as palladium on charcoal. p-Nitrobenzyl may also be cleaved by photolysis.

[0180] The 11- $\beta$ -hydroxy group may be masked as a carbonyl group. Thus a second such process comprises reduction of a compound of formula (XVI)



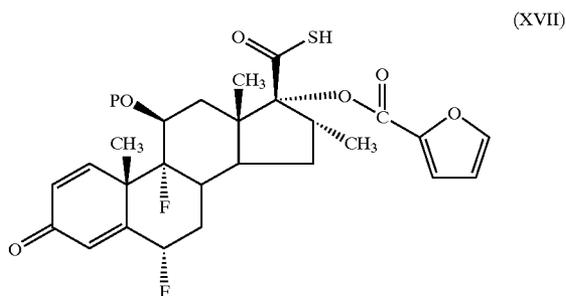
[0181] Reduction to the compound of formula (I) may be achieved eg by treatment with a hydride reducing agent such as borohydride eg sodium borohydride.

[0182] The 11-ketone (XVI) may also be masked. Examples of masked derivatives of compound of formula (XVI) include (i) ketal derivatives eg ketals formed by treatment of the compound of formula (XVI) with an alcohol eg methanol, ethanol or ethan-1,2-diol, (ii) dithioketal derivatives eg dithioketals formed by treatment of the compound of formula (XVI) with a thiol eg methanethiol, ethanethiol or ethan-1,2-dithiol, (iii) monothioketal derivatives eg monothioketals formed by treatment of the compound of formula (XVI) with eg 1-hydroxy-ethane-2-thiol, (iv) derivatives formed by treatment of the compound of formula (XVI) with an alcoholamine eg ephedrine, (v) imines formed by treatment of the compound of formula (XVI) with amines, (vi) oximes formed by treatment of compounds of formula (XVI) with hydroxylamines. We claims such derivatives of compound of formula (XVI) as an aspect of the invention.

[0183] These masked derivatives may be converted back to the ketone by conventional means eg ketals, imines and oximes are converted to carbonyl by treatment with dilute acid and dithioketals are converted to the ketone by a variety of methods as described by P. C. Bulman Page et al (1989), Tetrahedron, 45, 7643-7677 and references therein.

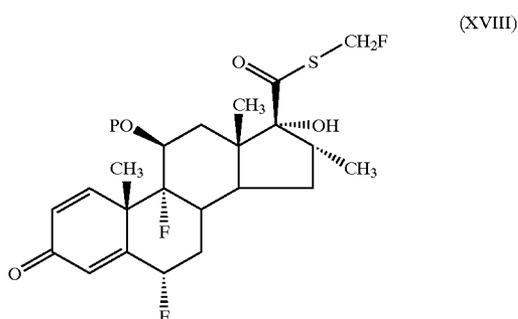
[0184] Compounds of formula (XV) may be prepared by a process comprising

[0185] (a) alkylating a compound of formula (XVII)



[0186] or a salt thereof wherein P represents a hydroxy protecting group; or

[0187] (b) esterifying a compound of formula (XVIII)



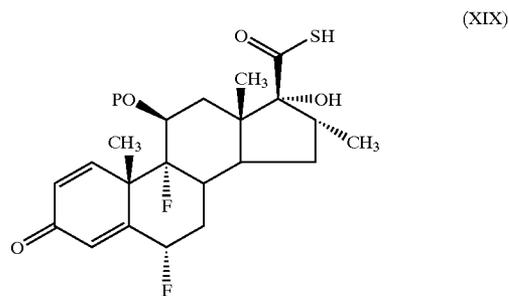
[0188] In step (a), analogous conditions to those described above for the conversion of a compound of formula (II) to a compound of formula (I) may be employed. Typically compound of formula (XVII) will be reacted with a compound of formula  $FCH_2L$  wherein L represents a leaving group (eg a halogen atom, a mesyl or tosyl group or the like) for example, an appropriate fluoromethyl halide under standard conditions. Preferably, the fluoromethyl halide reagent is bromofluoromethane.

[0189] In step (b), analogous conditions to those employed above for the conversion of a compound of formula (IX) to a compound of formula (VI) may be employed. For example, a suitable reagent would be an activated derivative of 2-furoic acid such as an activated ester or preferably a 2-furoyl halide eg 2-furoyl chloride in the presence of an organic base eg triethylamine.

[0190] Compound of formula (XVIII) may be prepared by alkylating the corresponding thioacid using methodology analogous to that already described (eg by reaction with a compound of formula  $FCH_2L$  wherein L represents a leaving group (eg a halogen atom, a mesyl or tosyl group or the like) for example, an appropriate fluoromethyl halide under standard conditions. Preferably, the fluoromethyl halide reagent is bromofluoromethane. The corresponding thioacids are

known compounds or may be prepared by standard methodology. Compound of formula (XVIII) may alternatively be prepared by protection of the corresponding hydroxy derivative.

[0191] Compound of formula (XVII) may be prepared by a process comprising esterifying a compound of formula (XIX)



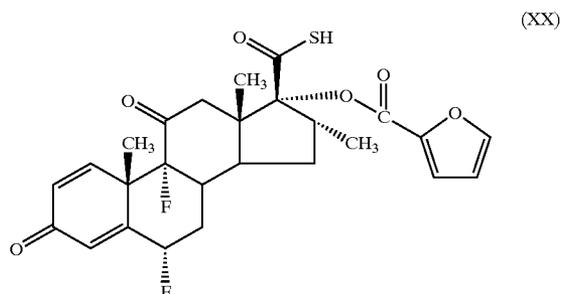
[0192] or a salt thereof wherein P represents a hydroxy protecting group.

[0193] This process may be performed using methodology analogous to that already described for the conversion of compounds of formula (III) to (II). For example, a suitable reagent would be an activated derivative of 2-furoic acid such as an activated ester or preferably a 2-furoyl halide eg 2-furoyl chloride in the presence of an organic base eg triethylamine.

[0194] Compounds of formula (XIX) may be prepared by protecting the corresponding hydroxy derivative (III), having first protected the thioacid which would then be deprotected.

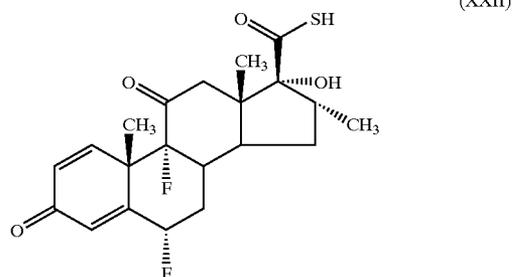
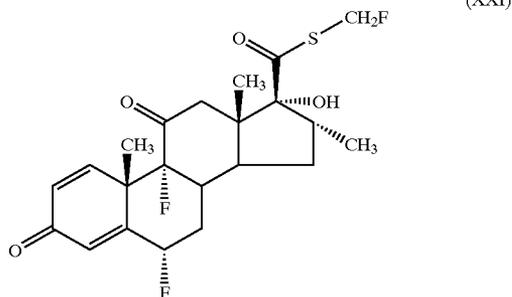
[0195] Compounds of formula (XVI) may be prepared by a process comprising

[0196] (a) alkylating a compound of formula (XX)



[0197] or a salt thereof or a derivative wherein the 11-carbonyl group is masked; or

[0198] (b) esterifying a compound of formula (XXI)<sup>o</sup>



[0199] or a derivative wherein the 11-carbonyl group is masked.

[0200] In step (a), analogous conditions to those described above for the conversion of a compound of formula (III) to a compound of formula (II) may be employed. Typically compound of formula (XX) will be reacted with a compound of formula  $FCH_2L$  wherein L represents a leaving group (eg a halogen atom, a mesyl or tosyl group or the like) for example, an appropriate fluoromethyl halide under standard conditions. Preferably, the fluoromethyl halide reagent is bromofluoromethane.

[0201] In step (b), analogous conditions to those employed above for the conversion of a compound of formula (IX) to a compound of formula (VI) may be employed. For example, a suitable reagent would be an activated derivative of 2-furoic acid such as an activated ester or preferably a 2-furoyl halide eg 2-furoyl chloride in the presence of an organic base eg triethylamine.

[0202] Compound of formula (XXI) or a derivative thereof wherein the 11-ketone group is masked may be prepared by alkylating the corresponding thioacid using methodology analogous to that already described (eg by reaction with a compound of formula  $FCH_2L$  wherein L represents a leaving group (eg a halogen atom, a mesyl or tosyl group or the like) for example, an appropriate fluoromethyl halide under standard conditions. Preferably, the fluoromethyl halide reagent is bromofluoromethane. The corresponding thioacids are known compounds or may be prepared from the corresponding carboxylic acids by methods analogous to those previously described.

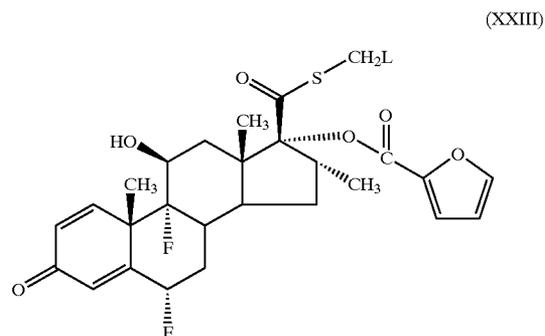
[0203] Compound of formula (XX) may be prepared by a process comprising esterifying a compound of formula (XXII)

[0204] or a derivative thereof wherein the 11-ketone group is masked.

[0205] This process may be performed using methodology analogous to that already described. For example, a suitable reagent would be an activated derivative of 2-furoic acid such as an activated ester or preferably a 2-furoyl halide eg 2-furoyl chloride in the presence of an organic base eg triethylamine.

[0206] Compounds of formula (XXII) and derivatives thereof wherein the 11-ketone is masked may be prepared by oxidation of the corresponding hydroxy derivative (IV) followed by masking of the ketone and subsequent conversion of the carboxylic acid group to the thioacid (see eg conversion of compounds of formula (IV) to (III)).

[0207] A further alternative process for the preparation of compounds of formula (I) or a solvate thereof comprises reaction of a compound of formula (XXIII)



[0208] wherein L represents a leaving group (eg halide other than fluoride such as chloride, iodide or a sulphonate ester such mesylate, tosylate, triflate) with a fluorine source.

[0209] Preferably the fluorine source is fluoride ion eg KF. Further details for this conversion may be obtained by reference to G. H. Phillipps et al., (1994) Journal of Medicinal Chemistry, 37, 3717-3729 or J Labelled Compd Radiopharm (1997) 39(7) 567-584.

[0210] Compounds of formula (XXIII) may be prepared by methods analogous to those described herein. Corresponding novel intermediates of formula (VI), (VIII), (IX), (IXA), (XV) and (XVI) wherein the —CH<sub>2</sub>F moiety is replaced with a —CH<sub>2</sub>L moiety (wherein L represents a leaving group other than fluorine) are claimed as an aspect of the invention.

[0211] A further alternative process for the preparation of compounds of formula (I) or a solvate thereof comprises deprotection or unmasking of a derivative of a compound of formula (I) in which the 3-carbonyl group is protected or masked.

[0212] The 3-carbonyl group may be masked in a manner analogous to that described above in relation to masking of the 11-carbonyl position. Thus the 3-carbonyl may be masked eg as a ketal, monothioketal, dithioketal, derivative with an alcoholamine, oxime or imine. The carbonyl group may be recovered by conventional means eg ketals are converted to carbonyl by treatment with dilute acid and dithioketals are converted to the ketone by a variety of methods as described by P. C. Bulman Page et al (1989), Tetrahedron, 45, 7643-7677 and references therein.

[0213] Certain intermediate compounds are new and we provide these, together where appropriate with their salts and solvates, as an aspect of the invention.

[0214] As noted above, we provide as a particular aspect of the invention a process for preparing a compound of formula (I) in unsolvated form which comprises:

[0215] (a) Crystallising the compound of formula (I) in the presence of a non-solvating solvent such as ethanol, methanol, water, ethyl acetate, toluene, methylisobutylketone or mixtures thereof; or

[0216] (b) Desolvating a compound of formula (I) in solvated form (eg in the form of a solvate with acetone, propan-2-ol, methylethylketone, DMF or tetrahydrofuran) eg by heating.

[0217] In step (b) the desolvation will generally be performed at a temperature exceeding 50° C. preferably at a temperature exceeding 100° C. Generally heating will be performed under vacuum.

[0218] There is also provided a compound of formula (I) in unsolvated form obtainable by the aforementioned process.

[0219] There is also provided as a particular aspect of the invention a process for preparing a compound of formula (I) as unsolvated Form 1 polymorph which comprises dissolving compound of formula (I) in methylisobutylketone, ethyl acetate or methyl acetate and producing compound of formula (I) as unsolvated Form 1 by addition of a non-solvating anti-solvent such as iso-octane or toluene.

[0220] According to a first preferred embodiment of this process the compound of formula (I) may be dissolved in ethyl acetate and compound of formula (I) as unsolvated Form 1 polymorph may be obtained by addition of toluene as anti-solvent. In order to improve the yield, preferably the ethyl acetate solution is hot and once the toluene has been added the mixture is distilled to reduce the content of ethyl acetate.

[0221] According to a second preferred embodiment of this process the compound of formula (I) may be dissolved in methylisobutylketone and compound of formula (I) as unsolvated Form 1 polymorph may be obtained by addition of iso-octane as anti-solvent.

[0222] There is also provided a compound of formula (I) as unsolvated Form 1 polymorph obtainable by the aforementioned processes.

[0223] A process for preparing a compound of formula (I) as unsolvated Form 2 polymorph comprises dissolving compound of formula (I) in unsolvated form in methanol or dry dichloromethane and recrystallising the compound of formula (I) as unsolvated Form 2 polymorph. Typically the compound of formula (I) will be dissolved in hot in methanol or dry dichloromethane and allowed to cool.

[0224] There is also provided a compound of formula (I) as unsolvated Form 2 polymorph obtainable by the aforementioned process.

[0225] A process for preparing a compound of formula (I) as unsolvated Form 3 polymorph comprises dissolving compound of formula (I) in particular as the acetone solvate in dichloromethane in the presence of water (typically 1-3% water by volume) and recrystallising the compound of formula (I) as unsolvated Form 3 polymorph.

[0226] There is also provided a compound of formula (I) as unsolvated Form 3 polymorph obtainable by the aforementioned process.

[0227] The advantages of the compound of formula (I) and/or its solvates or polymorphs may include the fact that the substance appears to demonstrate excellent anti-inflammatory properties, with predictable pharmacokinetic and pharmacodynamic behaviour, with an attractive side-effect profile, long duration of action, and is compatible with a convenient regime of treatment in human patients, in particular being amendable to once-per day dosing. The advantages may be appreciated in particular when the compound of formula (I) and/or its solvates or polymorphs are employed in combination with a the long-acting 2-adreno-receptor agonist. Further advantages may include the fact that the substance has desirable physical and chemical properties which allow for ready manufacture and storage.

#### BRIEF DESCRIPTION OF THE FIGURES

[0228] FIG. 1: Overlay of the XRPD profiles of Form 1, Form 2 and Form 3 polymorphs of unsolvated Compound of formula (I)

[0229] FIG. 2: Overlay of the XRPD profiles of Form 1, Form 2 and a 50:50 mixture of Form 1 and Form 2 polymorphs of unsolvated Compound of formula (I) together with the time dependence of the profile of the 50:50 mixture of Form 1 and Form 2

[0230] FIG. 3: DSC and TGA profiles of Form 1 polymorph of Unsolvated Compound of formula (I)

[0231] FIG. 4: Temperature dependence of the XRPD profile of Compound of formula (I) Unsolvated Form 3 obtained at 5 timepoints

[0232] FIG. 5: Temperature and time profile for the XRPD experiments of FIG. 4

[0233] FIGS. 6 to 9 relate to a dry powder inhalers;

[0234] FIG. 10 relates to a metered dose inhaler,

[0235] FIG. 6 shows a suitable medicament carrier in the form of a capsule;

[0236] FIG. 7a Is a cross-sectional side elevation of a suitable elongate medicament blister strip;

[0237] FIG. 7b is a top perspective of the medicament blister strip illustrated in FIG. 6a;

[0238] FIG. 8 shows a cross-sectional dry powder inhaler (DPI) comprising a powder reservoir;

[0239] FIG. 9 shows a cross-sectional dry powder inhaler (DPI) comprising an elongate medicament blister strip.

[0240] The medicament carrier in FIG. 6 is in the form of a capsule 1 comprising a wall 2 enclosing medicament powder 5. Medicament powder 5 is released on piercing the wall 2 of capsule 1 and may be inhaled by a patient.

[0241] FIG. 7a shows a sectional side-elevation of a single blister strip 106 comprising a pocket 107, containing dry powder 105, base 110 and lid comprising laminates 114, 115. The lid is composed of a metallic foil laminate 114 bound to a plastic laminate 115. In the diagram, the lid 114, 115 is hermetically sealed to base 110 by appropriate means (e.g. adhesion, welding). Base 110 comprises an organic polymeric plastic 103. A top perspective view of the blister strip 106 showing pockets 107 is illustrated in FIG. 7b. Laminated lid 114, 115 is sealed to base 110.

[0242] FIG. 8 shows a sectional view of a dry powder inhaler 420 for dispensing medicament in accord with the present invention. The inhaler 420 comprises a body 421 which defines a reservoir 423 and a reservoir cover 424. The reservoir contains a supply of medicament in dry powder form 405. The walls 423 of the reservoir, defined by the body 421, are comprised of a plastic material 403. Base 425 and body 421 define an aperture 430 through which powder 405 can pass from the reservoir to the dosing member 432. Powder 405 is guided by the walls 423 of the reservoir, which form a hopper, to the dosing member 432. Extending laterally from the lower end of the main body 421 is mouthpiece 435, through which the patient inhales via passage 433. If the device were intended for nasal inhalation this would be replaced by a nosepiece.

[0243] FIG. 9 shows a simplified cross-sectional plan view of a dry powder inhaler comprising an elongate medicament carrier suitable for dispensing medicament in accord with the present invention. The inhaler 540 dispenses unit doses of medicament powder from a medicament blister strip 506. The inhaler is comprised of an outer casing 544 enclosing a medicament strip 506 within body 521. The medicament strip may be, for example, any of those described in FIGS. 2a to 2b above. The patient uses the inhaler by holding the device to his mouth, depressing lever 538, and inhaling through mouthpiece 535. Depression of lever 538 activates the internal mechanism of the inhaler, such that the lid 514 and base 510 sheets of coiled medicament blister strip 506 are separated at index wheel 541 by use of contracting wheel 542 and base wheel 543. A unit dose of powdered medicament within blister pocket 507 is released and may be inhaled by the patient through exit port 533 and mouthpiece 535.

[0244] FIG. 10 is a schematic representation of a section through a standard metered dose inhalation device.

[0245] The standard metered dose inhaler shown in FIG. 10 comprises a housing 10 in which an aerosol canister 20 can be located. The housing is open at one end (which will hereinafter be considered to be the top of the device for convenience of description) and is closed at the other. An outlet 30 leads laterally from the closed end of the housing 10. In the embodiment illustrated, the outlet 30 is in the form of a mouthpiece intended for insertion into the mouth of the patient but it may, if desired, be designed as a nozzle for insertion into the patient's nostril.

[0246] The aerosol canister 20, comprising a neck region 21 and ferrule 22, has an outlet valve stem 40 at one end. This valve member can be depressed to release a measured dose from the aerosol canister or, alternatively, the valve stem 40 can be fixed and the main body of the canister can be moved relative to the valve member to release the dose.

[0247] As shown in FIG. 10, the aerosol canister 20 is located in the housing 10 so that one end protrudes from its open top, the canister being positioned such that the neck 21 and valve ferrule 22 are enclosed within housing 10. Spacer ribs (not shown) may be provided inside the housing to hold the external surface of the canister 20 spaced from the internal surface of the housing 10. A support 50 is provided at the lower end of the housing 10 and has a passage 60 in which the valve stem 40 of the aerosol canister 20 can be located and supported. A second passage 70 is provided in the support 50 and is directed towards the interior of the outlet 30. Thus, when the parts are in the positions shown in FIG. 1, the protruding portion of the aerosol canister 20 can be depressed to move the canister relative to the valve stem 40 to open the valve and a dose of medicament contained in the aerosol will be discharged through the passage 70 and into the outlet 30 from which it can be inhaled by a patient. One dose will be released from the aerosol canister each time it is fully depressed.

[0248] The body 6 is made from a plastic material and defines a housing 9 and a dispensing nozzle 11. The housing 9 defines a cavity formed by a side wall and a first end wall and a second end wall 14. The dispensing nozzle 11 is connected to and extends away from the second end wall 14 and has an external tapering form.

[0249] The following non-limiting Examples illustrate the invention:

#### EXAMPLES

[0250] General

[0251] <sup>1</sup>H-nmr spectra were recorded at 400 MHz and the chemical shifts are expressed in ppm relative to tetramethylsilane. The following abbreviations are used to describe the multiplicities of the signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets) and b (broad). Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module. LCMS was conducted on a Supelcosil LCABZ+ PLUS column (3.3 cm×4.6 mm ID) eluting with 0.1% HCO<sub>2</sub>H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO<sub>2</sub>H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0% B, 0.74-2

min 100% B, 4.2-5.3 min 0% B, 5.3-5.5 min 0% B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

[0252] DSC and TGA profiles were obtained using a Netzsch STA449C simultaneous thermal analyser using an unsealed pan with nitrogen gas flow and a thermal gradient of 10° C./min.

[0253] The moisture sorption characteristics were obtained using a Hiden Igasorb water sorption microbalance. The programme provides for stepwise increase in relative humidity (RH) from 0 to 90% RH and then decrease back to 0% RH in steps of 10% RH.

[0254] The XRPD analysis shown in FIGS. 1 and 2 were performed on a Phillips X'pert MPD powder diffractometer, serial number DY667. The method runs from 2 to 45 degrees 2Theta with 0.02 degree 2Theta step size and a 1 second collection time at each step. The XRPD analysis shown in FIG. 4 employed the same instrument with an Anton Parr TTK thermal accessory using a method running from 2 to 35 degrees 2Theta with 0.04 degree 2Theta step size and a 1 second collection time.

[0255] Intermediates

Intermediate 1: 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[2-furanylcarbonyloxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid

[0256] A solution of 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ , 17 $\alpha$ -dihydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid (prepared in accordance with the procedure described in GB 2088877B) (18 g, 43.64 mmol) in anhydrous dichloromethane (200 ml) and triethylamine (15.94 ml, 114 mmol) was treated at <5° C. with a solution of 2-furoyl chloride (11.24 ml, 114 mmol) in anhydrous dichloromethane (100 ml) over approximately 40 min. The solution was stirred at <5° C. for 30 min. The resulting solid was collected by filtration, washed successively with 3.5% aqueous sodium hydrogen carbonate solution, water, 1 M hydrochloric acid, and water and dried in vacuo at 60° C. to give a cream coloured solid. The dichloromethane filtrate was washed successively with 3.5% sodium hydrogen carbonate solution, water, 1 M hydrochloric acid, water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give a cream coloured solid which was combined with that isolated above. The combined solids (26.9 g) were suspended in acetone (450 ml) and stirred. Diethylamine (16.8 ml, 162 mmol) was added and the mixture stirred at room temperature for 4.5 h. The mixture was concentrated and the precipitate collected by filtration and washed with a little acetone. The washings and filtrate were combined, concentrated and loaded onto a silica gel Biotage column which was eluted with 24:1 chloroform:methanol. Fractions which contained the more polar component were combined and evaporated to give a cream coloured solid. This was combined with the solid isolated above and dried in vacuo to give a pale beige coloured solid (19.7 g). This was dissolved in warm water, the pH adjusted to 2 with concentrated hydrochloric acid and the mixture extracted with ethyl acetate. The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give, after drying at 50° C., the title compound as a cream coloured solid (18.081 g, 82%): LCMS retention time 3.88 min, m/z 507 MH<sup>+</sup>, NMR  $\delta$  (CDCl<sub>3</sub>) includes 7.61 (1H, m), 7.18-7.12 (2H, m), 6.52 (1H,

dd, J<sub>4</sub>, 2 Hz), 6.46 (1H, s), 6.41 (1H, dd, J<sub>10</sub>, 2 Hz), 5.47 and 5.35 (1H, 2 m), 4.47 (1H, bd, J=9 Hz), 3.37 (1H, m), 1.55 (3H, s), 1.21 (3H, s), 1.06 (3H, d, J 7 Hz).

Intermediate 1: 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyloxy)-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid (First Alternative Method)

[0257] A stirred suspension of 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ , 17 $\alpha$ -dihydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid (prepared in accordance with the procedure described in GB 2088877B) (1 wt, 49.5 g) in acetone (10 vol), 2.1 eq), keeping the temperature below 5° C., and stirred for 5 min at 0-5° C. 2-Furoyl chloride (0.65 wt, 2.05 eq) is then added over a minimum of 20 min, maintaining a reaction temperature at 0-5° C. The reaction is stirred for 30 min at 0-5° C. then sampled for analysis by HPLC. A solution of diethanolamine (1.02 wt, 4 eq) in methanol (0.8 vol) is added over ca 15 min followed by a line wash of methanol (0.2 vol) and the reaction stirred at 0-5° C. for 1 h. The reaction is again sampled for analysis by HPLC then warmed to approximately 20° C. and treated with water (1.1 wt). The reaction mixture is then treated with a solution of HCl (SG1.18 (11.5M), 1 vol) in water (10 vol) over ca 20 min maintaining a reaction temperature below 25° C. The suspension is stirred at 20-23° C. for at least 30 minutes then filtered. The filter cake is washed with water (3x2 vol). The product is dried in vacuo at approximately 60° C. overnight to give the title compound as a white solid (58.7 g, 96.5%).

Intermediate 1: 6 $\alpha$ , 9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyloxy)-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid (Second Alternative Method)

[0258] A stirred suspension of 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ ,17 $\alpha$ -dihydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid (prepared in accordance with the procedure described in GB 2088877B) (1 wt, 49.5 g) in acetone (10 vol) is cooled to 0-5° C. and treated with triethylamine (0.51 wt, 2.1 eq), keeping the temperature below 5° C., and stirred for 5 min at 0-5° C. 2-Furoyl chloride (0.65 wt, 2.05 eq) is then added over a minimum of 20 min, maintaining a reaction temperature at 0-5° C. The reaction mixture is stirred for at least 30 minutes and diluted with water (10 vol) maintaining a reaction temperature in the range 0-5° C. The resultant precipitate is collected by filtration and washed sequentially with acetone/water (50/50 2 vol) and water (2x2 vol). The product is dried under vacuum at approximately 55° C. overnight to leave 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyloxy)-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -yl S-(2-furanylcarbonyl)thioanhydride as a white solid (70.8 g, 98.2%) (NMR  $\delta$ (CD<sub>3</sub>CN) 0.99 (3H, d) (J=7.3 Hz), 1.24 (3H, s), 1.38 (1H, m) (J=3.9 Hz), 1.54 (3H, s), 1.67 (1H, m), 1.89 (1H, broad d) (J=15.2 Hz), 1.9-2.0 (1H, m), 2.29-2.45 (3H, m), 3.39 (1H, m), 4.33 (1H, m), 4.93 (1H, broad s), 5.53 (1H, ddd) (J=6.9, 1.9 Hz; J<sub>HF</sub>=50.9 Hz), 6.24 (1H, m), 6.29 (1H, dd) (J=10.3, 2.0 Hz), 6.63 (2H, m), 7.24-7.31 (3H, m), 7.79 (1H, dd) (J=<1 Hz), 7.86 (1H, dd) (J=<1 Hz)). A portion of the product (0.56 g) is mixed with 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ ,17 $\alpha$ -dihydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid (0.41 g) in a 1:1 molar ratio in DMF (10

volumes wrt total steroid input). The reaction mixture is treated with triethylamine (approximately 2.1 equivalents) and the mixture is stirred at approximately 20° C. for approximately 6 hours. Water (50 vol) containing excess conc HCl (0.5 vol) is added to the reaction mixture and the resultant precipitate collected by filtration. The bed is washed with water (2x5 vol) and dried in vacuo at approximately 55° C. overnight to leave the title compound as a white solid (0.99 g, 102%).

Intermediate 1A: 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanyl-carbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid Diisopropylethylamine Salt

[0259] A stirred suspension of 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ ,17 $\alpha$ -dihydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid (prepared in accordance with the procedure described in GB 2088877B) (49.5 g) in methylacetate (500 ml) is treated with triethylamine (35 ml) maintaining a reaction temperature in the range 0-5° C. 2-Furoyl chloride (25 ml) is added and the mixture stirred at 0-5° C. for 1 hour. A solution of diethanolamine (52.8 g) in methanol (50 ml) is added and the mixture stirred at 0-5° C. for at least 2 hours. Dilute hydrochloric acid (approx 1 M, 550 ml) is added maintaining a reaction temperature below 15° C. and the mixture stirred at 15° C. The organic phase is separated and the aqueous phase is back extracted with methyl acetate (2x250 ml). All of the organic phases are combined, washed sequentially with brine (5x250 ml) and treated with diisopropylethylamine (30 ml). The reaction mixture is concentrated by distillation at atmospheric pressure to an approximate volume of 250 ml and cooled to 25-30° C. (crystallisation of the desired product normally occurs during distillation/subsequent cooling). Tertiary butyl methyl ether (TBME) (500 ml) is added, the slurry further cooled and aged at 0-5° C. for at least 10 minutes. The product is filtered off, washed with chilled TBME (2x200 ml) and dried under vacuum at approximately 40-50° C. (75.3 g, 98.7%). NMR (CDCl<sub>3</sub>)  $\delta$ : 7.54-7.46 (1H, m), 7.20-7.12 (1H, dd), 7.07-6.99 (1H, dd), 6.48-6.41 (2H, m), 6.41-6.32 (1H, dd), 5.51-5.28 (1H, dddd<sup>2</sup>J<sub>H-F</sub> 50 Hz), 4.45-4.33 (1H, bd), 3.92-3.73 (3H, bm), 3.27-3.14 (2H, q), 2.64-2.12 (5H, m), 1.88-1.71 (2H, m), 1.58-1.15 (3H, s), 1.50-1.38 (15H, m), 1.32-1.23 (1H, m), 1.23-1.15 (3H s), 1.09-0.99 (3H, d).

Intermediate 1B: 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanyl-carbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid Triethylamine Salt

[0260] A stirred suspension of Intermediate 1 (30 g) in ethylacetate (900 ml) is treated with triethylamine (1.05 molar equivalents, 8.6 ml) and the mixture is stirred at approximately 20° C. for 1.5 hours. The precipitate is filtered off, washed with ethylacetate (2x2 vol) and dried in vacuo at 45° C. for 18 hours to give title compound as a white solid (28.8 g, 80%). NMR (CDCl<sub>3</sub>)  $\delta$ : 7.59-7.47 (1H, m), 7.23-7.13 (1H, dd), 7.08-6.99 (1H, d), 6.54-6.42 (2H, m), 6.42-6.32 (1H, dd), 5.55-5.26 (1H, dddd<sup>2</sup>J<sub>H-F</sub> 50 Hz), 4.47-4.33 (1H, bd), 3.88-3.70 (1H, bm), 3.31-3.09 (6H, q), 2.66-2.14 (5H, m), 1.93-1.69 (2H, m), 1.61-1.48 (3H, s), 1.43-1.33 (9H, t), 1.33-1.26 (1H, m), 1.26-1.15 (3H, s), 1.11-0.97 (3H, d).

## EXAMPLES

### Example 1

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid S-fluoromethyl Ester Unsolvated Form 1

[0261] A suspension of Intermediate 1 (2.5 g, 4.94 mmol) was dissolved in anhydrous N,N-dimethylformamide (25 ml) and sodium hydrogen carbonate (465 mg, 5.53 mmol) was added. The mixture was stirred at -20° C. and bromofluoromethane (0.77 ml, 6.37 mmol) was added and the mixture was stirred at -20° C. for 2 h. Diethylamine (2.57 ml, 24.7 mmole) was added and the mixture stirred at -20° C. for 30 min. The mixture was added to 2M hydrochloric acid (93 ml) and stirred for 30 min. Water (300 ml) was added and the precipitate was collected by filtration, washed with water and dried in vacuo at 50° C. to give a white solid which was recrystallised from acetone/water (to yield the acetone solvate of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester) and dried in vacuo at 50° C. to give the title compound (2.351 g, 88%): LCMS retention time 3.66 min, m/z 539 MH<sup>+</sup>, NMR  $\delta$  (CDCl<sub>3</sub>) includes 7.60 (1H, m), 7.18-7.11 (2H, m), 6.52 (1H, dd, J=4.2 Hz), 6.46 (1H, s), 6.41 (1H, dd, J10, 2 Hz), 5.95 and 5.82 (2H dd, J51, 9 Hz), 5.48 and 5.35 (1H, 2 m), 4.48 (1H, m), 3.48 (1H, m), 1.55 (3H, s), 1.16 (3H, s), 1.06 (3H, d, J=7 Hz).

### Example 1

6 $\alpha$ , 9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl Ester Unsolvated Form 1 (First Alternative Method)

[0262] A mobile suspension of Intermediate 1A (12.61 g, 19.8 mmol; equivalent to 10 g of Intermediate 1) in ethyl acetate (230 ml) and water (50 ml) is treated with a phase transfer catalyst (benzyltributylammonium chloride, 10 mol %), cooled to 3° C. and treated with bromofluoromethane (1.10 ml, 19.5 mmol, 0.98 equivalents), washing in with prechilled (0° C.) ethyl acetate (EtOAc) (20 ml). The suspension is stirred overnight, allowing to warm to 17° C. The aqueous layer is separated and the organic phase is sequentially washed with 1 M HCl (50 ml), 1% w/v NaHCO<sub>3</sub> solution (3x50 ml) and water (2x50 ml). The ethylacetate solution is distilled at atmospheric pressure until the distillate reaches a temperature of approximately 73° C. at which point toluene (150 ml) is added. Distillation is continued at atmospheric pressure until all remaining EtOAc has been removed (approximate distillate temperature 103° C.). The resultant suspension is cooled and aged at <10° C. and filtered off. The bed is washed with toluene (2x30 ml) and the product oven dried under vacuum at 60° C. to constant weight to yield the title compound (8.77 g, 82%).

### Example 1

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl Ester Unsolvated Form 1 (Second Alternative Method)

[0263] A suspension of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanyl-carbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,

4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester acetone solvate (prepared eg according to Example 11) (50.0 g) in acetone (1500 ml) and water (75 ml) was heated to reflux. The resultant mixture was clarified by hot filtration (Whatman 54 filter paper) during which time some solid crystallised in the filtrate. Further acetone (200 ml) was added to the filtrate giving a bright solution at reflux. The solution was distilled at atmospheric pressure until turbidity was noted whilst at reflux (approx 750 ml solvent collected). Toluene (1000 ml) was added to the hot solution and distillation at atmospheric pressure was continued giving crystallisation at a temperature of approximately 98° C. Distillation of solvent was continued until a reaction temperature of 105° C. was achieved (approximately 945 ml solvent collected). The mixture was cooled to ambient temperature, further cooled and aged at <10° C. for 10 minutes. The product was filtered off, washed with toluene (150 ml) and sucked dry. The product was dried at approximately 60° C. under vacuum for 16 h to leave the title compound as a dense white solid (37.8 g, 83.7%).

[0264] The XRPD pattern of Example 1 product is shown in FIG. 1. The DSC and TGA profiles are shown in FIG. 3.

#### Example 2

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl Ester Unsolvated Form 2

[0265] A suspension of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester (prepared for example according to Example 1, first method) (6.0 g) in dichloromethane (180 ml) was heated to reflux giving a bright solution. The solution was clarified by hot filtration (Whatman 54 filter paper) and the solution was distilled at atmospheric pressure (approx 100 ml solvent collected) giving crystallisation at reflux. The mixture was held at reflux for approximately 30 minutes and slowly cooled to ambient temperature. The mixture was further cooled and aged at 10-20° C. for 2 hours. The slurry was cooled to below 10° C. and the product was filtered off, sucked dry and dried at approximately 60° C. under vacuum overnight to leave a white solid (4.34 g, 71%).

[0266] A more pure sample of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester unsolvated Form 2 was obtained by a cooling crystallisation of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester (prepared eg according to Example 1, first method) in methanol (60 volumes, distilled at atmospheric pressure to approx 37.5 volumes). The product was isolated by filtration and oven dried at 60° C. under vacuum for 16 hours to leave a white, electrostatic solid (4.34 g, 71%).

[0267] The XRPD pattern of Example 2 product is shown in FIG. 1.

#### Example 3

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid S-fluoromethyl Ester

[0268] Unsolvated Form 3

[0269] A suspension of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester acetone solvate (prepared eg according to Example 11) (20.0 g) in dichloromethane (800 ml, 40 volumes) and water (10 ml, 0.5 volumes) was heated to reflux giving a bright solution. The solution was clarified by hot filtration (Whatman 54 filter paper) during which time some solid crystallised in the filtrate which was fully dissolved upon heating to reflux. The solution was distilled at atmospheric pressure (approx 400 ml solvent collected) and allowed to cool to ambient temperature. The mixture was further cooled and aged at <10° C. for 10 minutes. The product was filtered off, sucked dry and dried at approximately 60° C. under vacuum overnight to leave a white solid (12.7 g, 70%).

[0270] The XRPD pattern of Example 3 product is shown in FIG. 1 and FIG. 4.

#### Example 4

Interconversion of Forms 1, 2 and 3 of Unsolvated 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid S-fluoromethyl Ester

[0271] Slurring a mixture of Form 1 and Form 2 in water at ambient temperature revealed that the components are transformed entirely to Form 1 with time. XRPD results are shown in FIG. 2. Similar results were obtained by slurring a mixture of Form 1 and Form 2 in ethanol at ambient temperature. From these results it may be concluded that Form 1 is the thermodynamically more stable polymorphic form out of the two forms.

[0272] Thermal XRPD studies on Form 3 were performed as shown in FIG. 4. The temperature and time profile is shown in FIG. 5 and the 5 traces shown in FIG. 4 were obtained at the equilibration points shown in FIG. 5. The results indicate that Form 3 is converted first to Form 2 and then to Form 1 as temperature is elevated.

#### Example 5

Moisture sorption of Forms 1, 2 and 3 of Unsolvated 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl Ester

[0273] The moisture sorption characteristics of the three forms were determined by monitoring the weight change of solid when exposed to stepwise increased and then decreased humidity. The results obtained were as follows:

[0274] Form 1: uptake of 0.18% w/w of moisture over the range 0-90% relative humidity at 25° C.

[0275] Form 2: uptake of 1.1-2.4% w/w of moisture over the range 0-90% relative humidity at 25° C.

[0276] Form 3: uptake of 1.2-2.5% w/w of moisture over the range 0-90% relative humidity at 25° C.

#### Example 6

Enthalpy of dissolution of Forms 1 and 3 of unsolvated 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl Ester

[0277] Enthalpies of dissolution in DMSO and acetonitrile were determined at 25° C. The results were as follows:

	Form 1	Form 3
Acetonitrile	+13.74	+8.62
DMSO	+1.46	-5.21
(results in kJ/mol)		

[0278] Form these results it may be determined that the enthalpy of transition from Form 3 to Form 1 is approximately 5.1-6.7 kJ/mol. On the assumption that the entropy of transition is small, since both Forms are unsolvated, the enthalpy of transition may be equated with the free energy of transition. Thus these data suggest that Form 1 is the thermodynamically most stable form at 25° C.

#### Example 7

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl Ester Methyleneacetone Solvate

[0279] A suspension of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester (prepared eg according to Example 1) (400 mg) in methylethylketone (3.2 ml) is heated to reflux giving a clear solution. A portion of the solvent is distilled off at atmospheric pressure (approx 1 ml) and the mixture cooled to approximately 20° C. The crystallised product is filtered off, dried at approximately 20° C. under vacuum to leave the title compound as a white solid (310 mg, 68%). NMR  $\delta$  (CDCl<sub>3</sub>) includes the peaks described in Example 1 for the parent compound and the following additional solvent peaks: 2.45 (2H, q), 2.14 (3H, s), 1.06 (3H, t).

#### Example 8

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid S-fluoromethyl Ester Isopropanol Solvate

[0280] A solution of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester (prepared eg according to Example 1) (150 mg) in isopropanol (15 ml) is left to slowly crystallise over a period of approximately 8 weeks. The resultant chunky crystals are isolated by filtration to leave the title compound as a white solid. NMR  $\delta$  (CDCl<sub>3</sub>) includes the peaks described in Example 1 for the parent compound and the following additional solvent peaks: 4.03 (1H, m), 1.20 (6H, d).

#### Example 9

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid S-fluoromethyl ester Tetrahydrofuran Solvate

[0281] A suspension of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester (prepared eg according to Example 1) (150 mg) in THF (20 vol) is warmed to give a clear solution. The solvent is allowed to slowly evaporate over a period of 6 days to leave title compound as a white solid. Alternatively, the THF solution is added dropwise to solution of potassium bicarbonate (2% w/w) in water (50 vol) and the precipitated product collected by filtration to furnish the title compound as a white solid. NMR  $\delta$  (CDCl<sub>3</sub>) includes the peaks described in Example 1 for the parent compound and the following additional solvent peaks: 3.74 (4H, m), 1.85 (4H, m).

#### Example 9

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid S-fluoromethyl Ester Tetrahydrofuran Solvate (Alternative Method)

[0282] A mobile suspension of 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid triethylamine salt (prepared eg according to Intermediate 1B) (1.2 g) in THF (10 ml) is treated with a phase transfer catalyst (tetrabutylammonium bromide, typically between 8 and 14 mol %), cooled to approximately 3° C. and treated with bromofluoromethane (0.98 equivalents). The suspension is stirred for between 2 and 5 hours, allowing to warm to 17° C. The reaction mixture is poured into water (30 vol), stirred at approximately 10° C. for 30 minutes and filtered off. The collected solid is washed with water (4x3 vol) and the product oven dried under vacuum at 60° C. overnight to give the title compound as a white solid (0.85 g, 87%).

#### Example 10

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester DMF solvate

[0283] A mixture of Intermediate 1 (4.5 g, 8.88 mmol) in DMF (31 ml) is treated with potassium bicarbonate (0.89 g, 8.88 mmol) and the mixture is cooled to -20° C. A solution of bromofluoromethane (0.95 g, 8.50 mmol, 0.98 eqv.) in DMF (4.8 ml) at 0° C. is added and the mixture is stirred at -20° C. for 4 hours. The mixture is then stirred at -20° C. for a further 30 minutes, added to 2M hydrochloric acid (100 ml) and stirred for a further 30 minutes at 0-5° C. The precipitate collected by vacuum filtration, washed with water and dried at 50° C. to give the title compound (4.47 g, 82%). NMR  $\delta$  (CD<sub>3</sub>OD) includes the peaks described in Example 1 for the parent compound and the following additional solvent peaks: 7.98 (1H, bs), 2.99 (3H, s), 2.86 (3H, s).

## Example 11

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl Ester Acetone Solvate

[0284] A solution of Intermediate 1 (530.1 g, 1 wt) in dimethylformamide (DMF) (8 vol) is treated with potassium hydrogen carbonate (0.202 wt, 1.02 eq) and the mixture cooled to  $-17\pm 3^\circ$  C. with stirring. Bromofluoromethane (BFM) (0.22 wt, 0.99 eq) is then added and the reaction stirred at  $-17\pm 3^\circ$  C. for at least 2 h. The reaction mixture is then added to water (17 vol) at  $5\pm 3^\circ$  C. over ca 10 min followed by a water (1 vol) line wash. The suspension is stirred at  $5-10^\circ$  C. for at least 30 min and then filtered. The filter cake (the DMF solvate of 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester) is washed with water (4 $\times$ 4 vol) and the product is pulled dry on the filter. The damp cake is returned to the vessel, acetone (5.75 vol) added and heated at reflux for 2 h. The mixture is cooled to  $59\pm 3^\circ$  C. and water (5.75 vol) added, keeping temperature at  $52\pm 3^\circ$  C. The mixture is then cooled to  $20\pm 3^\circ$  C., filtered and dried in vacuo at  $60\pm 5^\circ$  C. overnight to give the title compound as a white solid (556.5 g, 89%). NMR  $\delta$  (CDCl<sub>3</sub>) includes the peaks described in Example 1 for the parent compound and the following additional solvent peaks: 2.17 (6H, s).

## Example 12

Dry Powder Composition Containing 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid S-fluoromethyl Ester, Unsolvated Form 1

[0285] A dry powder formulation was prepared as follows:

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester, unsolvated Form 1 (prepared according to Example 1, first alternative method and micronised to a MMD of 3 $\mu$ m):	0.20 mg
milled lactose (wherein not greater than 85% of particles have a MMD of 60–90 $\mu$ m, and not less than 15% of particles have a MMD of less than 15 $\mu$ m):	12 mg

[0286] A peelable blister strip containing 60 blisters each filled with a formulation as just described was prepared.

## Example 12A

Dry Powder Composition Containing 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid S-fluoromethyl Ester, Unsolvated Form 1, and a long Acting  $\beta_2$ -Adrenoreceptor Agonist

[0287] A dry powder formulation may be prepared as follows:

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester, unsolvated Form 1 (prepared according to Example 1, first alternative method and micronised to a MMD of 3 $\mu$ m):	0.20 mg
Long-acting $\beta_2$ -adrenoreceptor agonist (micronised to a MMD of 3 $\mu$ m):	0.02 mg
milled lactose (wherein not greater than 85% of particles have a MMD of 60–90 $\mu$ m, and not less than 15% of particles have a MMD of less than 15 $\mu$ m):	12 mg

[0288] A peelable blister strip containing 60 blisters each filled with a formulation as just described may be prepared.

## Example 13

Aerosol Formulation Containing 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid S-fluoromethyl Ester, Unsolvated Form 1

[0289] An aluminium canister was filled with a formulation as follows:

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester, Unsolvated Form 1 (prepared according to Example 1, first alternative method) and micronised to a MMD of 3 $\mu$ m):	250 $\mu$ g
1,1,1,2-tetrafluoroethane:	to 50 $\mu$ l
(amounts per actuation)	

[0290] in a total amount suitable for 120 actuations and the canister was fitted with a metering valve adapted to dispense 50  $\mu$ l per actuation.

## Example 13A

Aerosol Formulation Containing 6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic Acid S-fluoromethyl Ester, Unsolvated Form 1, and a Long Acting  $\beta_2$ -Adrenoreceptor Agonist

[0291] An aluminium canister may be filled with a formulation as follows:

6 $\alpha$ ,9 $\alpha$ -Difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-fluoromethyl ester, Unsolvated Form 1 (prepared according to Example 1, first alternative method) and micronised to a MMD of 3 $\mu$ m):	250 $\mu$ g
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-continued

Long-acting $\beta_2$ -adrenoreceptor agonist (micronised to a MMD of 3 $\mu\text{m}$ ):	25 $\mu\text{g}$
1,1,1,2-tetrafluoroethane: (amounts per actuation)	to 50 $\mu\text{l}$

[0292] in a total amount suitable for 120 actuations and the canister may be fitted with a metering valve adapted to dispense 50  $\mu\text{l}$  per actuation.

#### [0293] Pharmacological Activity

##### [0294] In Vitro Pharmacological Activity

[0295] Pharmacological activity was assessed in a functional in vitro assay of glucocorticoid agonist activity which is generally predictive of anti-inflammatory or anti-allergic activity in vivo.

[0296] For the experiments in this section, compound of formula (I) was used as unsolvated Form 1.

[0297] The functional assay was based on that described by K. P. Ray et al., *Biochem J.* (1997), 328, 707-715. A549 cells stably transfected with a reporter gene containing the NF- $\kappa$ B responsive elements from the ELAM gene promoter coupled to sPAP (secreted alkaline phosphatase) were treated with test compounds at appropriate doses for 1 hour at 37° C. The cells were then stimulated with tumour necrosis factor (TNF, 10 ng/ml) for 16 hours, at which time the amount of alkaline phosphatase produced is measured by a standard colourimetric assay. Dose response curves were constructed from which EC<sub>50</sub> values were estimated.

[0298] In this test the compound of Example 1 showed an EC<sub>50</sub> value of <1 nM. The glucocorticoid receptor (GR) can function in at least two distinct mechanisms, by upregulating gene expression through the direct binding of GR to specific sequences in gene promoters, and by downregulating gene expression that is being driven by other transcription factors (such as NF $\kappa$ B or AP-1) through their direct interaction with GR.

[0299] In a variant of the above method, to monitor these functions, two reporter plasmids have been generated and introduced separately into A549 human lung epithelial cells by transfection. The first cell line contains the firefly luciferase reporter gene under the control of a synthetic promoter that specifically responds to activation of the transcription factor NF $\kappa$ B when stimulated with TNF $\alpha$ . The second cell line contains the renilla luciferase reporter gene under the control of a synthetic promoter that comprises 3 copies of the consensus glucocorticoid response element, and which responds to direct stimulation by glucocorticoids. Simultaneous measurement of transactivation and transrepression was conducted by mixing the two cell lines in a 1:1 ratio in 96 well plate (40,000 cells per well) and growing overnight at 37° C. Test compounds were dissolved in DMSO, and added to the cells at a final DMSO concentration of 0.7%. After incubation for 1 h 0.5 ng/ml TNF $\alpha$  (R&D Systems) was added and after a further 15 hours at 37° C.,

the levels of firefly and renilla luciferase were measured using the Packard Firelite kit following the manufacturers' directions. Dose response curves were constructed from which EC<sub>50</sub> values were determined.

	Transactivation (GR) ED <sub>50</sub> (nM)	Transrepression (NF $\kappa$ B) ED <sub>50</sub> (nM)
Compound of Formula (I)	0.06	0.20
Metabolite (X)	>250	>1000
Fluticasone propionate	0.07	0.16

##### [0300] In Vivo Pharmacological Activity

[0301] Pharmacological activity in vivo was assessed in an ovalbumin sensitised Brown Norway rat eosinophilia model. This model is designed to mimic allergen induced lung eosinophilia, a major component of lung inflammation in asthma.

[0302] For the experiments in this section, compound of formula (I) was used as unsolvated Form 1.

[0303] Compound (I) produced dose dependant inhibition of lung eosinophilia in this model after dosing as an intratracheal (IT) suspension in saline 30 min prior to ovalbumin challenge. Significant inhibition is achieved after a single dose of 30  $\mu\text{g}$  of compound (1) and the response was significantly (p=0.016) greater than that seen with an equivalent dose of fluticasone propionate in the same study (69% inhibition with compound (I) vs 41% inhibition with fluticasone propionate).

[0304] In a rat model of thymus involution 3 daily IT doses of 100  $\mu\text{g}$  of compound (I) induced significantly smaller reductions in thymus weight (p=0.004) than an equivalent dose of fluticasone propionate in the same study (67% reduction of thymus weight with compound (I) vs 78% reduction with fluticasone propionate).

[0305] Taken together these results indicate a superior therapeutic index for compound (I) compared to fluticasone propionate.

##### [0306] In Vitro Metabolism in Rat and Human Hepatocytes

[0307] Incubation of compound (I) with rat or human hepatocytes shows the compound to be metabolised in an identical manner to fluticasone propionate with the 17- $\beta$  carboxylic acid (X) being the only significant metabolite produced. Investigation of the rate of appearance of this metabolite on incubation of compound (I) with human hepatocytes (37° C., 10  $\mu\text{M}$  drug concentration, hepatocytes from 3 subjects, 0.2 and 0.7 million cells/mL) shows compound (I) to be metabolised ca. 5-fold more rapidly than fluticasone propionate:—

Subject number	Cell density (million cells/mL)	17- $\beta$ acid metabolite production (pmol/h)	
		Compound (I)	Fluticasone propionate
1	0.2	48.9	18.8
1	0.7	73.3	35.4
2	0.2	118	9.7
2	0.7	903	23.7
3	0.2	102	6.6
3	0.7	580	23.9

Median metabolite production 102–118 pmol/h for compound (I) and 18.8–23.0 pmol/h for fluticasone propionate.

**[0308]** Pharmacokinetics after Intravenous (Iv) and Oral Dosing in Rats

**[0309]** Compound (I) was dosed orally (0.1 mg/kg) and IV (0.1 mg/kg) to male Wistar Han rats and pharmacokinetic parameters determined. Compound (I) showed negligible oral bioavailability (0.9%) and plasma clearance of 47.3 mL/min/kg, approaching liver blood flow (plasma clearance of fluticasone propionate=45.2 mL/min/kg).

**[0310]** Pharmacokinetics after Intra-Tracheal Dry Powder Dosing in the Pig.

**[0311]** Anaesthetised pigs (2) were dosed intra-tracheally with a homogenous mixture of compound (I) (1 mg) and fluticasone propionate (1 mg) as a dry powder blend in lactose (10% w/w). Serial blood samples were taken for up to 8 h following dosing. Plasma levels of compound (I) and fluticasone propionate were determined following extraction and analysis using LC-MS/MS methodology, the lower limits of quantitation of the methods were 10 and 20  $\mu$ g/mL for compound (I) and fluticasone propionate respectively. Using these methods compound (I) was quantifiable up to 2 hours after dosing and fluticasone propionate was quantifiable up to 8 hours after dosing. Maximum plasma concentrations were observed for both compounds within 15 min after dosing. Plasma half-life data obtained from IV dosing (0.1 mg/kg) was used to calculate AUC (0-inf) values for compound (I). This compensates for the plasma profile of Compound (I) only being defined up to 2 hours after an IT dose and removes any bias due to limited data between compound (I) and fluticasone propionate.

**[0312]**  $C_{max}$  and AUC (0-inf) values show markedly reduced systemic exposure to compound (I) compared to fluticasone propionate:—

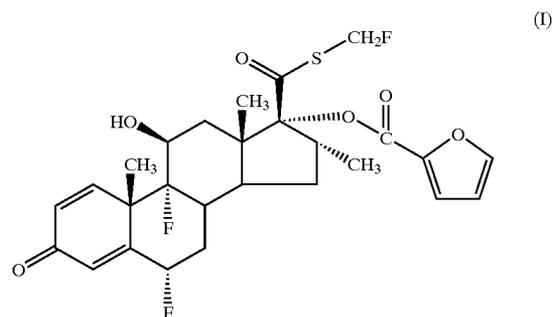
	$C_{max}$ (pg/mL)		AUC (0-inf) (hr · pg/mL)	
	Pig 1	Pig 2	Pig 1	Pig 2
Compound of Formula (I)	117	81	254	221
Fluticasone propionate	277	218	455	495

**[0313]** The pharmacokinetic parameters for both compound (I) and fluticasone propionate were the same in the anaesthetised pig following intravenous administration of a mixture of the two compounds at 0.1 mg/kg. The clearance of these two glucocorticoids is similar in this experimental pig model.

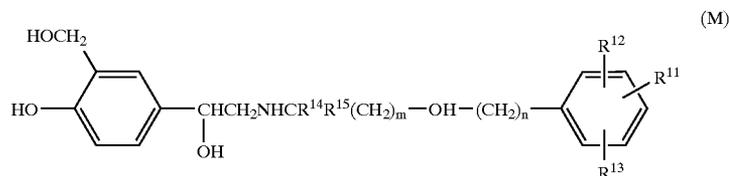
**[0314]** Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

**[0315]** The patents and patent applications described in this application are herein incorporated by reference.

1. A pharmaceutical formulation for administration by inhalation comprising a compound of formula (I),



or a solvate thereof, together with a long-acting  $\beta_2$ -adrenoreceptor agonist, wherein the  $\beta_2$ -adrenoreceptor agonist is a compound of the formula (M):



or a salt or solvate thereof, wherein:

m is an integer of from 2 to 8.

n is an integer of from 3 to 11.

with the proviso that m+n is 5 to 19,

R<sup>11</sup> is —XSO<sub>2</sub>NR<sup>16</sup>R<sup>17</sup> wherein X is —(CH<sub>2</sub>)<sub>p</sub>- or C<sub>2-6</sub> alkenylene;

R<sup>16</sup> and R<sup>17</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C(O)NR<sup>18</sup>R<sup>19</sup>, phenyl, and phenyl (C<sub>1-4</sub>alkyl)-,

or R<sup>16</sup> and R<sup>17</sup>, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and R<sup>16</sup> and R<sup>17</sup> are each optionally substituted by one or two groups selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>alkoxy, hydroxy-substituted C<sub>1-6</sub>alkoxy, —CO<sub>2</sub>R<sup>18</sup>, —SO<sub>2</sub>NR<sup>18</sup>R<sup>19</sup>, —CONR<sup>18</sup>R<sup>19</sup>, —NR<sup>18</sup>C(O)R<sup>19</sup>, or a 5-, 6- or 7-membered heterocyclic ring,

R<sup>18</sup> and R<sup>19</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl,

C<sub>3-6</sub>cycloalkyl, phenyl, and phenyl (C<sub>1-4</sub>alkyl)-; and

p is an integer of from 0 to 6, preferably from 0 to 4;

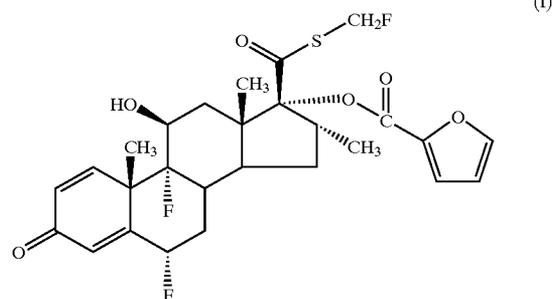
R<sup>12</sup> and R<sup>13</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, halo, phenyl, and C<sub>1-6</sub>haloalkyl; and

R<sup>14</sup> and R<sup>15</sup> are independently selected from hydrogen and C<sub>1-4</sub>alkyl with the proviso that the total number of carbon atoms in R<sup>14</sup> and R<sup>15</sup> is not more than 4,

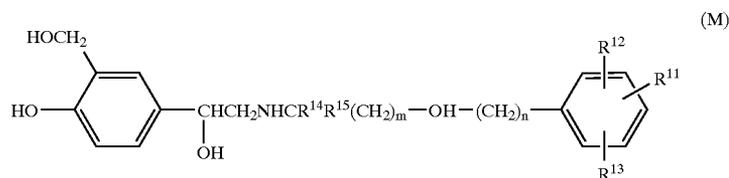
8. A method of treatment of an inflammatory disorder of the respiratory tract once-per-day which comprises administration of a pharmaceutical formulation according to claim 1.

9. A method of treatment according to claim 8 wherein the inflammatory disorder of the respiratory tract is asthma.

10. An inhaler containing a plurality of doses of a pharmaceutical formulation comprising a compound of formula (I)



or a solvate thereof, together with a long-acting β<sub>2</sub>-adrenoreceptor agonist, wherein the β<sub>2</sub>-adrenoreceptor agonist is a compound of the formula (M):



which formulation has a therapeutically useful effect in the treatment of inflammatory disorders of the respiratory tract over a period of 24 hours or more.

2. A pharmaceutical formulation according to claim 1 wherein the compound of formula (I) or a solvate thereof and the long-acting β<sub>2</sub>-adrenoreceptor agonist are both present in particulate form.

3. A pharmaceutical formulation according to claim 2 further comprising a particulate carrier.

4. A pharmaceutical formulation according to claim 3 wherein the carrier is lactose.

5. A pharmaceutical formulation according to claim 1 further comprising a liquified propellant gas.

6. A pharmaceutical formulation according to claim 1 wherein the inflammatory disorder of the respiratory tract is asthma.

7. (canceled)

or a salt or solvate thereof, wherein:

m is an integer of from 2 to 8.

n is an integer of from 3 to 11,

with the proviso that m+n is 5 to 19,

R<sup>11</sup> is —XSO<sub>2</sub>NR<sup>16</sup>R<sup>17</sup> wherein X is —(CH<sub>2</sub>)<sub>p</sub>- or C<sub>2-6</sub> alkenylene;

R<sup>16</sup> and R<sup>17</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C(O)NR<sup>18</sup>R<sup>19</sup>, phenyl, and phenyl (C<sub>1-4</sub>alkyl)-,

or R<sup>16</sup> and R<sup>17</sup>, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and R<sup>16</sup> and R<sup>17</sup> are each optionally substituted by one or two groups selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>alkoxy, hydroxy-substituted C<sub>1-6</sub>alkoxy, —CO<sub>2</sub>R<sup>18</sup>, —SO<sub>2</sub>NR<sup>18</sup>R<sup>19</sup>, —CONR<sup>18</sup>R<sup>19</sup>, —NR<sup>18</sup>C(O)R<sup>19</sup>, or a 5-, 6- or 7-membered heterocyclic ring,

R<sup>18</sup> and R<sup>19</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl, phenyl, and phenyl (C<sub>1-4</sub>alkyl)-; and

p is an integer of from 0 to 6, preferably from 0 to 4;

R<sup>12</sup> and R<sup>13</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, halo, phenyl, and C<sub>1-6</sub>haloalkyl; and

R<sup>14</sup> and R<sup>15</sup> are independently selected from hydrogen and C<sub>1-6</sub>alkyl with the proviso that the total number of carbon atoms in R<sup>14</sup> and R<sup>15</sup> is not more than 4,

which formulation has a therapeutically useful effect in the treatment of inflammatory disorders of the respiratory tract over a period of 24 hours or more, and which doses are suitable for once-per-day administration of the formulation by inhalation.

**11.** An inhaler according to claim 10 wherein the compound of formula (I) or a solvate thereof and the long-acting  $\beta_2$ -adrenoreceptor agonist are both present in particulate form.

**12.** An inhaler according to claim 10 wherein the formulation further comprises a particulate carrier.

**13.** An inhaler according to claim 12 wherein the carrier is lactose.

**14.** An inhaler according to claim 10 wherein the formulation further comprises a liquefied propellant gas.

**15.** (canceled)

**16.** An inhaler according to claim 10 wherein the inflammatory disorder of the respiratory tract is asthma.

**17-19.** (canceled)

**20.** A method for the treatment of a human or animal subject with an anti-inflammatory and/or allergic condition, which method comprises administering to said human or animal subject an effective amount of a formulation as claimed in claim 1.

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