

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
12 February 2009 (12.02.2009)

PCT

(10) International Publication Number
WO 2009/019598 A2

(51) International Patent Classification:

A61K 31/502 (2006.01)

(21) International Application Number:

PCT/IB2008/002133

(22) International Filing Date: 8 August 2008 (08.08.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

1718/CHE/2007 3 August 2007 (03.08.2007) IN

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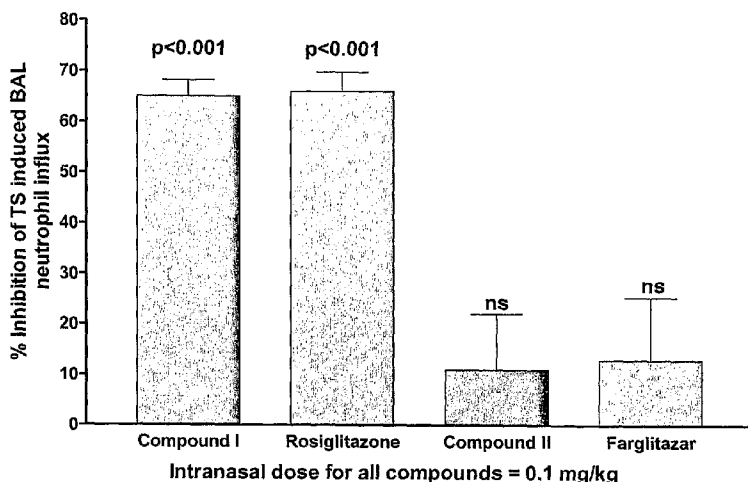
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID,

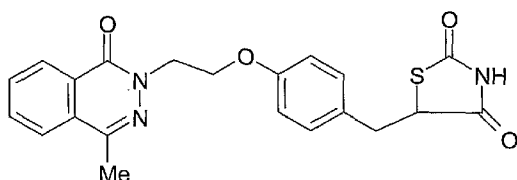
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(54) Title: INHALATION THERAPY FOR RESPIRATORY DISORDERS

FIG. 1:



(57) Abstract: The present invention relates to a novel method of preventing and treating respiratory disorders, such as asthma, COPD, cystic fibrosis and pulmonary fibrosis, in a subject by administering to the subject a compound (I) having the structure: or its pharmaceutically acceptable salt thereof and/or its polymorph thereof



(I)



IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- without international search report and to be republished upon receipt of that report
- with information concerning request for restoration of the right of priority in respect of one or more priority claims

INHALATION THERAPY FOR RESPIRATORY DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to Indian application number. 1718/CHE/2007 filed on August 3, 2007, the contents of which are incorporated herein in their entirety by reference.

BACKGROUND OF THE INVENTION

[0002] The present invention relates generally to the use of a PPAR γ agonist compound, especially when administered directly to the lungs by inhalation via the mouth or nose, for the treatment and prevention of respiratory disorders. The invention also relates to polymorphic forms of that compound for such use.

[0003] A broad spectrum of respiratory diseases and disorders has been recognized, many of which have overlapping and interacting etiologies. Two of the most widespread and prevalent of these diseases are chronic obstructive pulmonary disorder (COPD) and asthma. Respiratory diseases have a significant inflammatory component. For example, current therapy for COPD and severe asthma focuses mainly on the reduction of symptoms using short and long acting bronchodilators either as monotherapies or combinations of long acting β_2 agonist bronchodilators with inhaled corticosteroids (ICS). The disappointing anti-inflammatory data for ICS either alone or in combination with β_2 agonists has intensified the search for an effective anti-inflammatory drug for COPD.

[0004] COPD is a chronic inflammatory disorder that involves complex interactions between cells of the innate and acquired immune response both in the lung and potentially also systemically. One hypothesis under investigation is whether novel, demonstrably anti-inflammatory agents can halt or slow function decline characteristic of COPD. Reducing the frequency and severity of exacerbations has become an increasingly important target for COPD therapy as the prognosis for patients following exacerbations is poor. Anti-inflammatory therapy in COPD, and in asthma, is expected to reduce the frequency and severity of exacerbations, improve quality of life and perhaps

reduce decline in lung function. Effective anti-inflammatory therapy in COPD may also produce an improvement in lung function.

[0005] Peroxisome Proliferation Receptor gamma receptor (PPAR γ) agonists are a class of drug which increase sensitivity to glucose in diabetic patients and currently two PPAR γ agonists are approved for clinical use in diabetes; Rosiglitazone and Pioglitazone. See Campbell IW, *Curr Mol Med*. 2005 May;5(3):349-63. Both of these compounds are thiazolidinediones (TZDs), and are, in practice, administered by the oral route for systemic delivery. Physiological activation of PPAR γ is believed to increase the sensitivity of peripheral tissues to insulin, thus facilitating the clearance of glucose from the blood and producing the desired anti-diabetic effect.

[0006] Unfortunately, PPAR γ agonists also have unwanted cardiovascular effects, including haemodilution, peripheral and pulmonary oedema, and congestive heart failure (CHF). CHF is a complex clinical syndrome characterized by exertional dyspnea, fatigue and, often, peripheral edema resulting from left ventricular dysfunction (LVR). These unwanted effects are also believed to result from activation of PPAR γ . In particular, a significant effort has been devoted to investigating the hypothesis that PPAR γ agonists disturb the normal maintenance of fluid balance via binding to the PPAR γ receptor in the kidney. See Guan *et al*, *Nat Med*. 2005;11(8):861-6 and Zhang *et al*, *Proc Natl Acad Sci USA*. 2005 28;102(26):9406-11. Treatment with PPAR γ agonists by the oral route for systemic delivery is also associated with an unwanted increase in body weight.

[0007] In addition to their effects on glucose metabolism, a variety of reports have been published which demonstrate the potential of specific PPAR γ agonists, such as Rosiglitazone, to exert anti-inflammatory effects. For instance, (i) Rosiglitazone has been reported to exert effects in diabetic patients consistent with an anti-inflammatory effect (Haffner *et al*, *Circulation*. 2002 Aug 6;106(6):679-84, Marx *et al*, *Arterioscler Thromb Vasc Biol*. 2003 Feb 1;23(2):283-8); (ii) Rosiglitazone has been reported to exert anti-inflammatory effects in a range of animal models of inflammation, including: carageenan-induced paw oedema (Cuzzocrea *et al*, *Eur J Pharmacol*. 2004 Jan 1;483(1):79-93), TNBS-induced colitis (Desreumanux *et al*, *J Exp Med*.

2001 Apr 2;193(7):827-38, Sanchez-Hidalgo *et al*, Biochem Pharmacol. 2005 Jun 15;69(12):1733-44), experimental encephalomyelitis (Feinstein *et al*, Ann Neurol. 2002 Jun;51(6):694-702) collagen-induced (Cuzzocrea *et al*, Arthritis Rheum. 2003 Dec;48(12):3544-56) and adjuvant-induced arthritis (Shiojiri *et al*, Eur J Pharmacol. 2002 Jul 19;448(2-3):231-8), carageenan-induced pleurisy (Cuzzocrea *et al*, Eur J Pharmacol. 2004 Jan 1;483(1):79-93), ovalbumin-induced lung inflammation (Lee *et al*, FASEB J. 2005 Jun;19(8):1033-5) and LPS-induced lung tissue neutrophilia (Birrell *et al*, Eur Respir J. 2004 Jul;24(1):18-23) and (iii) Rosiglitazone has been reported to exert anti-inflammatory effects in isolated cells, including iNOS expression in murine macrophages (Reddy *et al*, Am J Physiol Lung Cell Mol Physiol. 2004 Mar;286(3):L613-9), TNF α -induced MMP-9 activity in human bronchial epithelial cells (Hetzl *et al*, Thorax. 2003 Sep;58(9):778-83), human airway smooth muscle cell proliferation (Ward *et al*, Br J Pharmacol. 2004 Feb;141(3):517-25) and MMP-9 release by neutrophils (WO 0062766).

[0008] Based on observations of anti-inflammatory activity in cells relevant to the lung, the utility of PPAR γ agonists in general has been disclosed for the treatment of inflammatory respiratory disorders including asthma, COPD, cystic fibrosis, pulmonary fibrosis (Refer patent applications WO00/53601, WO02/13812 and WO00/62766). These disclosures include administration by both the oral and inhaled routes.

[0009] COPD patients are known to be at a higher risk than other clinical populations from congestive heart failure (CHF) (Curkendall *et al*, Ann Epidemiol, 2006;16: 63–70, Padeletti *et al*, Int J Cardiol. 2008;125(2):209-15) and so it is important that systemic activation of the PPAR γ receptors is kept to a minimum in these patients to avoid increasing the likelihood of CHF. Administering respiratory drugs by the inhaled route is one approach to target the lung with an anti-inflammatory agent whilst keeping systemic exposure of the drug low, reducing the likelihood of systemic activity and observation of side effects.

[0010] Therefore, taking into account the potential antiinflammatory utility of PPAR γ receptor agonists in the treatment of respiratory disease, and weighing that potential utility against the undesirable side effects of high

systemic exposure to this drug class, there is a need for PPAR γ receptor agonists that are effective in treating such diseases, have physico-chemical properties rendering them suitable for pulmonary delivery by inhalation, and have low systemic exposure following inhalation.

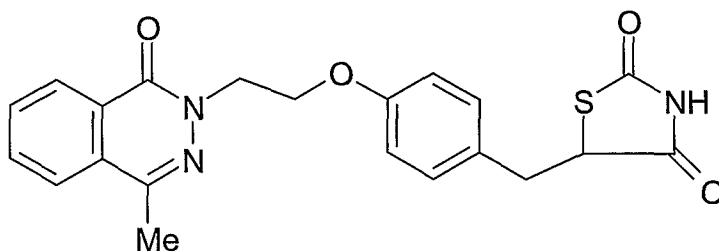
[0011] Systemic exposure of an inhaled drug is generally achieved by two methods. Following oral inhalation of a respiratory drug 10-50% of the dosage delivered by the device (e.g. inhaler or nebuliser) is delivered to the respiratory tract where it can achieve its desired pharmacological action in the lungs. Ultimately, any drug that has not been metabolized by the lungs, is delivered by the lungs to the systemic circulation. The other 50-90% of the inhaled dose is swallowed. Therefore, one method of reducing systemic exposure by an inhaled drug is for the drug to have reduced oral bioavailability (ability of the GI tract to absorb intact drug and deliver it to the circulation). Once the active drug is present in the circulation, the clearance rate of the drug is critical to its systemic activity. Therefore, another desired property of an inhaled drug for the treatment of lung disease is to have high systemic clearance to minimize systemic activity.

[0012] Molecules for delivery via the respiratory tract must be delivered in a suitable size, typically less than 10 micron, preferably less than 5 micron, to enable the drug to reach the airways of the lung. For many materials delivered as a suspension (e.g. in a metered dose inhaler or a suspension nebuliser formulation and those delivered via a dry powder inhaler) they are typically reduced in particle size from their normal form using common methods of micronization including, but not limited to microniser, typically by an air jet mill. Micronisation in an air jet mill is a highly energetic process and occurs by collision and impaction of the input particles with the components of the mill and other particles of material. The high energy in an air jet mill can cause material to undergo both chemical change (degradation) and physical change. It is generally recognised that materials with a high melting point will be less likely to undergo either chemical or physical changes compared to materials with a lower melting point. Therefore it is desirable that a compound intended for administration in micronised form by inhalation has a high melting point (>150 °C).

[0013] Following micronisation, particle size distribution (PSD) of the compound is examined and generally described in the art by specifying d10, d50 and d90 values. The average particle size, i.e. the average equivalent diameter, is defined as the diameter where 50 mass-% (of the particles) of the powder have a larger equivalent diameter, and the other 50 mass-% have a smaller equivalent diameter. Hence the average particle size is denoted as equivalent d50. For inhaled use a d50 of less than 10 microns, preferably less than 5 microns is desired.

[0014] However, different PSD profiles can result in a similar d50 values and so d10 and d90 values are also described. The d10 value is the equivalent diameter where 10 mass-% (of the particles) of the powder has a smaller diameter (and hence the remaining 90% is coarser). The definition of d90 can be derived similarly. For inhaled use, a d10 of <4 micron, and a d90 of <12 microns is generally desired. It is preferred that there are no particles larger than 12 microns present.

[0015] The compound 5-{4-[2-(4-methyl-1-oxo-1*H*-phthalazin-2-yl)-ethoxy] benzyl} thiazolidine-2,4-dione (alternatively named 5-{4-[2-(4-methyl-1-oxo-1,2-dihydro-phthalazin-2-yl)-ethoxy] phenylmethyl} thiazolidine-2,4-dione) having the structural formula:



(hereafter referred to as "Compound I") is known from Example 6 of International application WO98/45292 (US patent no. 6,011,036) to be useful in the treatment of diabetes. It has not been disclosed to be useful for the treatment of respiratory diseases such as asthma, COPD, steroid resistant asthma, severe asthma, cystic fibrosis, and pulmonary fibrosis.

[0016] The crystalline physical form in which Compound I is recovered when prepared according to Example 6 of International application WO98/45292 (US patent no. 6,011,036) has now been characterized by X-Ray Powder Diffraction (XRPD) and Fourier Transform Infra Red

Spectroscopy (FT-IR), as background to the present invention. That physical form of Compound I is hereafter referred to as "Form 0" or "Form 0 of Compound I".

SUMMARY OF THE INVENTION

[0017] In one aspect the present invention is directed to the use of Compound I or a pharmaceutically acceptable salt thereof and/or one or more polymorphic forms thereof, as an anti-inflammatory compound, useful for treatment of respiratory diseases when administered by inhalation.

[0018] In another aspect, the invention is directed to the identification of novel stable polymorphic forms of Compound I, different from Form 0 referred to above, suitable for formulation for inhaled administration, for treatment of respiratory diseases.

[0019] Thus, the invention relates to the use of Compound I, in some embodiments in a stable polymorphic form, for treatment of respiratory disease, to compositions for such treatment, and to such treatment in combination with treatments with other respiratory drugs.

BRIEF DESCRIPTION OF THE FIGURES

[0020] FIG. 1 is a bar graph that illustrates the effect of intranasal administration to laboratory mice of Compound I, and three other PPAR γ agonist compounds, referred to as Rosiglitazone, Compound II, and Farglitazar, (at 0.1 mg/kg) on the number of BAL neutrophils 24 hours post final exposure.

[0021] FIG. 2 is a bar graph that illustrates the effect of oral administration of Rosiglitazone, Compound II and Farglitazar (at 5 mg/kg) on the number of BAL neutrophils 24 hours post final exposure.

[0022] FIG. 3 shows the Differential Scanning Calorimetry (DSC) thermogram for another polymorphic form of Compound I, the preparation of which is described hereafter, and which is hereafter referred to as Form I of Compound I

[0023] FIG. 4 shows the X-ray powder diffraction pattern (XRPD) for Form I of Compound I

[0024] FIG. 5 shows the Fourier Transform Infra Red (FTIR) spectrum for Form I of Compound I

[0025] FIG. 6 shows the DSC thermogram for another polymorphic form of Compound I, the preparation of which is described hereafter, and which is hereafter referred to as Form II of Compound I

[0026] FIG. 7 shows the X-ray powder diffraction pattern for Form II of Compound I

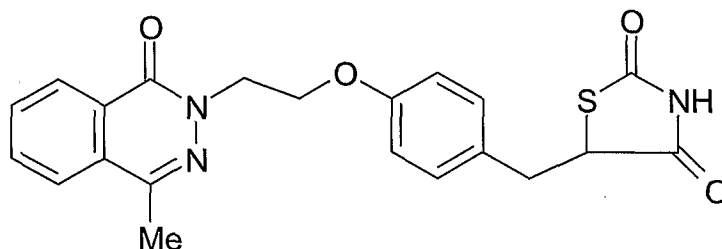
[0027] FIG. 8 shows the Fourier Transform Infra Red (FTIR) spectrum for Form II of Compound I

[0028] FIG. 9 shows the X-ray powder diffraction pattern for Form 0 of Compound I,

[0029] FIG. 10 shows the Fourier Transform Infra Red (FTIR) spectrum for Form 0 of Compound I,

DETAILED DESCRIPTION OF THE INVENTION

[0030] According to the present invention, there is provided the use of Compound I in the manufacture of a composition adapted for administration by inhalation via the mouth or nose, for treatment of a respiratory disorder, wherein Compound I has the structure:



[0031] The respiratory disorder may be one or more of asthma (mild, moderate or severe) e.g. bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, steroid resistant asthma, bronchitis including infectious and eosinophilic bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary fibrosis including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive

activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus, pulmonary edema, pulmonary embolism, pneumonia, pulmonary sarcoisosis, farmer's lung and related diseases; hypersensitivity pneumonitis, silicosis, respiratory failure, acute respiratory distress syndrome, emphysema, chronic bronchitis, and lung cancer. In particular, the methods and compositions of the present invention encompass the prevention and treatment of the respiratory disorder, COPD.

[0032] In another aspect, the invention provides a method of treating a respiratory disorder in a subject comprising administering an amount, effective to treat such disorder, of Compound I as defined above to the subject by inhalation via the mouth or nose.

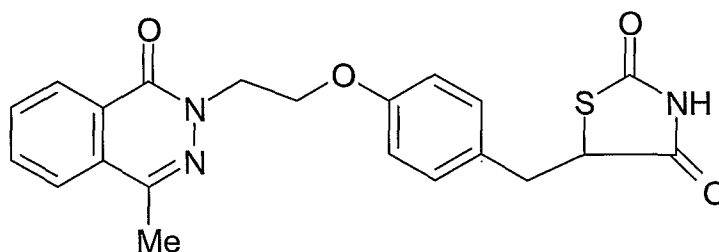
[0033] The invention also provides a pharmaceutical composition for treating respiratory disorders in a subject, the pharmaceutical composition being adapted for inhalation via the mouth or nose and comprising Compound I as defined above and one or more pharmaceutically acceptable carriers and/or excipients.

[0034] In any of its aspects, the invention includes use of Compound I in combination with a conventional respiratory treatment agent, such as a bronchodilator drug and/or another anti-inflammatory drug. Such combination therapy can be administered and presented by various modes of packages including but not limited to a kit, the said kit may comprise of one dosage form comprising of Compound I and a second dosage form comprising of a conventional respiratory treatment agent.

[0035] The present inventors found unexpectedly that not all PPAR γ agonists are useful for the treatment of chronic respiratory diseases such as COPD. This is in contrast to the general disclosures in many patent publications relating to anti-diabetic PPAR γ agonists, which appear to assume universal utility of the disclosed compounds in such diseases.

[0036] A range of PPAR γ agonists that have all shown activity in mouse models of diabetes were examined in a mouse model of COPD. Surprisingly, of the four compounds examined, only two were seen to have anti-inflammatory activity. This observation was made when the compounds were given to laboratory mice by a surrogate for the inhaled route for delivery to the lung. Compound I was identified with particularly potent anti-inflammatory activity.

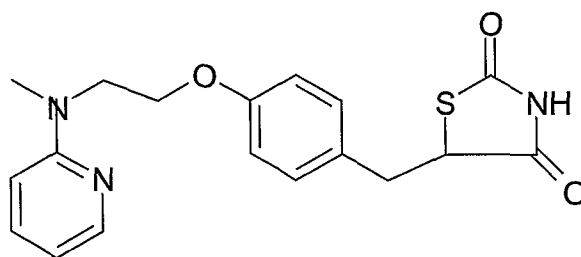
Compound I:



[0037] Compound I is disclosed in WO98/45292 (also US patent no. 6,011,036), but has not been disclosed to be useful for the treatment of respiratory diseases such as asthma, COPD, cystic fibrosis, and pulmonary fibrosis.

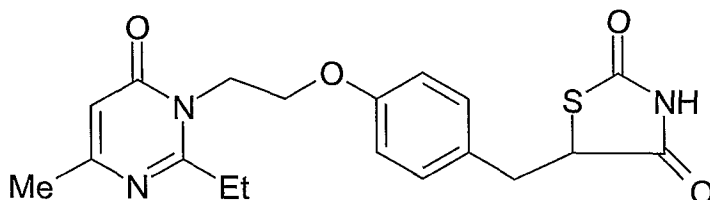
[0038] In this mouse model of COPD, the PPAR γ agonist, Rosiglitazone also demonstrated anti-inflammatory activity.

Rosiglitazone:

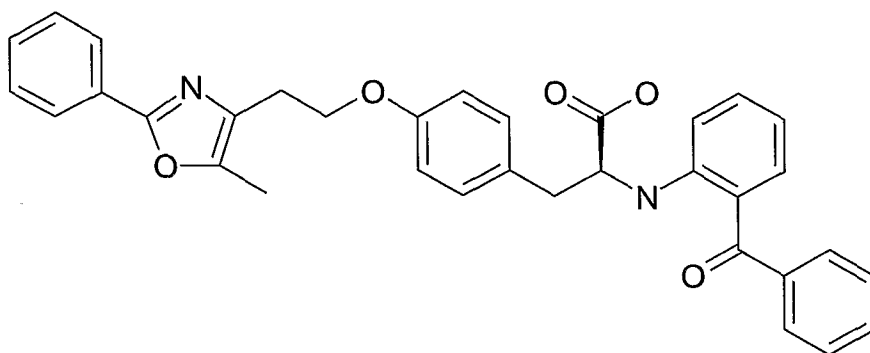


[0039] However, the two other PPAR γ agonists tested were not active in the mouse COPD model; namely, Compound II and Farglitazar.

Compound II (see Chakrabarti et al, *Diabetes, Obesity and Metabolism*, 2002, 4:319-328):



Farglitazar (also known as GI 262570, GW-262570, (2S)-((2-benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid):



[0040] To confirm this differential activity, the compounds inactive by the surrogate inhaled route (Compound II and Farglitazar) were administered by the oral route at the same doses that demonstrated activity in diabetes models. Surprisingly, both Compound II and Farglitazar did not display anti-inflammatory activity when given at a high dose by the oral route. In contrast, similar to the result when administered to the lungs by the surrogate inhaled route, Rosiglitazone demonstrated significant anti-inflammatory activity when administered orally.

[0041] Taken together, the results from these two experiments suggest that not all PPAR γ agonists, known as specific compounds or as members of a known class are useful for the treatment of respiratory diseases such as COPD, and the identification of such agonists, useful for respiratory disease, is not obvious from the literature relating to those compounds or classes of compounds. The present inventors have identified Compound I to be particularly active.

[0042] Compound I, when administered by a surrogate route for inhalation by mouth (intra-nasally at 0.1 mg/kg) inhibits tobacco smoke (TS) induced inflammatory cell recruitment in the lungs of a mouse model of

COPD. TS exposure is widely accepted to be the principal cause of COPD in human beings.

[0043] Rosiglitazone has been previously disclosed to be useful in the treatment of respiratory diseases such as COPD (WO00/62766) and, as mentioned above, has now also been found effective in the tobacco smoke mouse model of COPD. However, as described earlier, oral administration of a PPAR γ agonist will result in systemic drug activity of the agent leading to the known side effects of PPAR γ agonists, CHF in particular which is a significant disadvantage in COPD patients. Appreciation of this critical feature is not described in the prior art and no obvious preference for the inhaled route over oral administration is described.

[0044] Administration of Rosiglitazone by the inhaled route is unlikely to significantly reduce the risk of systemic activity and side effects as it is >99% bioavailable by the oral route, and following inhalation (50-90%) of the drug is swallowed. Compound I has lower oral bioavailability than Rosiglitazone [Example 3 below].

[0045] Furthermore, Rosiglitazone is a successful once daily oral drug for the treatment of diabetes, in part due to good systemic activity and average plasma clearance. As reduced systemic exposure is desired, a faster plasma clearance rate than Rosiglitazone is desired. Compound I has higher plasma clearance in both rat and dog than Rosiglitazone [Example 3 below].

[0046] Furthermore, Compound I in its Form II has a melting point (168-178 °C) which makes it more likely to be stable during the micronisation process necessary to reduce the input material to a size suitable for inhalation. In contrast, Rosiglitazone (base) has a melting point of 153 °C (*Brummond and Jianliang, Journal of Organic Chemistry; 1999, 64(5):1723-6*) and Rosiglitazone maleate (which is the marketed pharmaceutical form) has a melting point of 122-123 °C (*Derosa, Salvadeo and Cicero, Therapy, 2006, 3(5), 559-569*). It appears, therefore, that the higher melting point of Form II of Compound I compared with Rosiglitazone is advantageous in producing size reduced drug product for administration by inhalation.

[0047] Compound I may be administered by inhalation via the mouth or nose, for the treatment of a respiratory disease, at a dose that is effective in

reducing inflammation in the respiratory tract. The respiratory disease may be a chronic one, such as COPD, but also may be asthma (mild, moderate, severe, steroid resistant), cystic fibrosis, pulmonary fibrosis, or other inflammatory lung diseases.

[0048] Compound I may be administered to the subject by inhalation at a dose of about 0.1 µg to about 50 mg/day. In some embodiments, Compound I may be administered to the subject by inhalation at a dose of about 0.1 µg to about 5 mg/day.

[0049] Combination therapy, in which Compound I is administered with one or more respiratory disorder treatment agents other than a PPAR γ agonist, is useful for the purpose of preventing and treating respiratory disorders and respiratory disorder-related complications in a subject that is in need of such prevention and treatment.

[0050] As used herein, the term "subject" means mammals, such as humans and other animals, including horses, dogs, cats, rats, mice, sheep, pigs, etc. In exemplary embodiments, the subject may include subjects in which treatment and/or prevention of the conditions described herein would be beneficial.

[0051] For ease of reference, the present invention will be described in terms of administration to human subjects. It will be understood, however, that such descriptions are not limited to administration to humans, but will also include administration to other animals unless explicitly stated otherwise.

[0052] An additional advantage of delivering an anti-inflammatory therapy by the inhaled route for the treatment of respiratory disease is that it can be administered in combination with an inhaled bronchodilator drug. Bronchodilator therapies are first line treatments for chronic inflammatory diseases such as asthma and COPD and provide rapid symptomatic relief. In contrast, anti-inflammatories can have less pronounced immediate benefits which can hinder patient compliance, despite offering significant clinical benefits following chronic therapy. Inhaled combination therapy of an anti-inflammatory with a bronchodilator can improve compliance and this has been found with β 2 adrenergic agonist/glucocorticoid combination products such as

Advair®/Seretide® (salmeterol xinafoate/fluticasone propionate) and Symbicort® (formoterol fumarate/Budesonide).

[0053] The monotherapy and combination therapy of the present invention would be useful, for example, to reduce such respiratory disorder symptoms as, for example, coughing, inflammation, congestion, dyspnea, wheezing, hyperventilation, difficulty breathing, bronchospasm, and bronchoconstriction in a subject suffering from such symptoms. The monotherapy or combination therapy of the present invention would also be useful to prevent the occurrence of such symptoms.

[0054] As used herein, the phrases "combination therapy", "co-administration", "co-administering", "administration with", "administering", "combination", or "co-therapy", when referring to use of Compound I and a respiratory disorder treatment agent other than a PPAR γ agonist, are intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner. Thus, Compound I and a respiratory disorder treatment agent other than a PPAR γ agonist may be administered in one inhalable therapeutic dosage form, such as or in two or more separate therapeutic dosage forms, of which at least that containing Compound I is inhalable.

[0055] Sequential administration of such treatments encompasses both relatively short and relatively long periods between the administration of each of the drugs of the present method. However, for purposes of the present invention, the second drug is administered while the first drug is still having an efficacious effect on the subject. Thus, the present invention takes advantage of the fact that the simultaneous presence of the combination of Compound I and a respiratory disorder treatment agent other than a PPAR γ agonist in a subject has a greater efficacy than the administration of either agent alone.

[0056] In some embodiments, the second of the two drugs is to be given to the subject within the therapeutic response time of the first drug to be administered. For example, the present invention encompasses administration of Compound I to the subject and the later administration of a

respiratory disorder treatment agent, as long as the respiratory disorder treatment agent is administered to the subject while the Compound I is still present in the subject at a level, which in combination with the level of the respiratory disorder treatment agent is therapeutically effective, and vice versa.

[0057] As used herein, the terms "therapeutic response time" mean the duration of time that a compound is present or detectable within a subject's body.

[0058] As used herein, the term "monotherapy" is intended to embrace administration of Compound I to a subject suffering from a respiratory disorders or respiratory disorder-related complication as a single therapeutic treatment without an additional therapeutic treatment comprising a respiratory disorder treatment agent other than a PPAR γ agonist. However, the Compound I may still be administered in multiple dosage forms. Thus, the Compound I may be administered in one or more inhaled powder or aerosol doses.

[0059] As used herein, the terms "treating" or "to treat," mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms. The term "treatment" includes alleviation, elimination of causation of or prevention of respiratory disorders associated with, but not limited to, any of the diseases or disorders described herein.

[0060] In some embodiments, combination therapy in accordance with the invention may include the inhaled administration of Compound I in combination with bronchodilator medicines. As used herein, the term "bronchodilator" means a medicament that relaxes bronchial muscle resulting in expansion of the bronchial air passages. Included as bronchodilators are, without limitation, β 2 adrenergic agonists, such as albuterol, bambuterol, terbutaline, fenoterol, formoterol, formoterol fumarate, salmeterol, salmeterol xinafoate, arformoterol, arformoterol tartrate, indacaterol (QAB-149), carmoterol, picumeterol, BI 1744 CL, GSK159797, GSK59790, GSK159802, GSK642444, GSK678007, GSK96108, clenbuterol, procaterol, bitolterol, and brodxaterol, TA-2005 and also compounds of EP1440966, JP05025045,

WO93/18007, WO99/64035, US2002/0055651, US2005/0133417, US2005/5159448, WO00/075114, WO01/42193, WO01/83462, WO02/66422, WO02/70490, WO02/76933, WO03/24439, WO03/42160, WO03/42164, WO03/72539, WO03/91204, WO03/99764, WO04/16578, WO04/016601, WO04/22547, WO04/32921, WO04/33412, WO04/37768, WO04/37773, WO04/37807, WO04/39762, WO04/39766, WO04/45618, WO04/46083, WO04/71388, WO04/80964, EP1460064, WO04/087142, WO04/89892, EP01477167, US2004/0242622, US2004/0229904, WO04/108675, WO04/108676, WO05/033121, WO05/040103, WO05/044787, WO04/071388, WO05/058299, WO05/058867, WO05/065650, WO05/066140, WO05/070908, WO05/092840, WO05/092841, WO05/092860, WO05/092887, WO05/092861, WO05/090288, WO05/092087, WO05/080324, WO05/080313, US20050182091, US20050171147, WO05/092870, WO05/077361, DE10258695, WO05/111002, WO05/111005, WO05/110990, US2005/0272769, WO05/110359, WO05/121065, US2006/0019991, WO06/016245, WO06/014704, WO06/031556, WO06/032627, US2006/0106075, US2006/0106213, WO06/051373, WO06/056471;; and anticholinergic bronchodilators, such as ipratropium bromide, tiotropium, tiotropium bromide (Spiriva®), glycopyrrolate, NVA237, LAS34273, GSK656398, GSK233705, GSK 573719, LAS35201, QAT370 and oxytropium bromide. Other bronchodilators may include TA 2005 (i.e., 8-hydroxy-5-(1-hydroxy-2-2((2-(4-methoxy-phenyl)-1-methylethyl)amino)ethyl)-2(1H)-quinolinone) (for instance as the monohydrochloride), as well as anti-histamines (e.g., terfenadine).

[0061] In some embodiments, combination therapy may also involve the inhaled administration of Compound I in combination with other anti-inflammatory drugs, including but not limited to corticosteroids such as beclomethasone, beclomethasone (e.g., as the mono or the dipropionate ester), flunisolide, fluticasone (e.g. as the propionate or furoate ester), Ciclesonide, mometasone (e.g. as the furoate ester), mometasone desonide, rofleponide, hydrocortisone, prednisone, prednisolone, methyl prednisolone, naflocort, deflazacort, halopredone acetate, fluocinolone acetonide, fluocinonide, clocortolone, tipredane, prednicarbate, alclometasone dipropionate, halometasone, rimexolone, deprodone propionate,

triamcinolone, betamethasone, fludrocortisone, desoxycorticosterone, rofleponide, etiprendnol dicloacetate and the like. Steroid drugs may additionally include steroids in clinical or pre-clinical development for respiratory diseases such as GW-685698, GW-799943, NCX-1010, NCX-1020, NO-dexamethasone, PL-2146, NS-126 (formerly ST-126) and compounds referred to in international patent applications WO02/12265, WO02/12266, WO02/100879, WO03/062259, WO03/048181 and WO03/042229 WO02/88167, WO02/00679, WO03/35668, WO03/62259, WO03/64445, WO03/72592, WO04/39827 and WO04/66920;. Steroid drugs may also additionally include next generation molecules in development with reduced side effect profiles such as selective glucocorticoid receptor agonists (SEGRAs), including ZK-216348 and compounds referred to in international patent applications WO-00/032585, WO-00/0210143, WO-2005/034939, WO-2005/003098, WO-2005/035518 and WO-2005/035502 and functional equivalents and functional derivatives thereof.

[0062] The combinations of the invention may optionally comprise one or more additional active substances which are known to be useful in the treatment of respiratory disorders such as phosphodiesterase (PDE) 4 inhibitors (such as roflumilast), PDE5 inhibitors, PDE7 inhibitors, leukotriene D4 inhibitors, leukotriene B4 inhibitors, inhibitors of egfr-kinase, p38 MAP kinase inhibitors, NF-kB pathway inhibitors such as Ikk inhibitors, A2A adenosine receptor agonists, TNFalpha signalling inhibitors (such as ligand binding agents, receptor antagonists), Interleukin-1 signalling inhibitors, CRTH2 receptor antagonists, protease inhibitors (such as neutrophil elastase inhibitors, MMP inhibitors, Cathepsin inhibitors), IL-8 signalling molecules, CXCR1 inhibitors, CXCR2 inhibitors, iNOS modulators, anti-oxidants (including N-acetylcysteine and superoxide dismutase mimetics), HMG-CoA reductase inhibitors (statins); for example rosuvastatin, mevastatin, lovastatin, simvastatin, pravastatin and fluvastatin; Mucus regulators such as INS-37217, diquafosol, sibenadet, CS-003, talnetant, DNK-333, MSI-1956, gefitinib; and/or NK-1 receptor antagonists.

[0063] In one aspect, the invention provides for the use of inhaled administration of the Compound I in combination with other anti-inflammatory drugs and bronchodilator drug combinations (i.e. triple combination product),

including but not limited to salmeterol xinafoate/fluticasone propionate (Advair/Seretide®), formoterol fumarate/budesonide (Symbicort®), formoterol fumarate/mometasone furoate, formoterol fumarate/beclometasone dipropionate (Foster®), formoterol fumarate/fluticasone propionate (FlutiForm®), Indacaterol/mometasone furoate, Indacaterol/QAE-397, GSK159797/GSK 685698, GSK159802/GSK 685698, GSK642444/GSK 685698, formoterol fumarate/ciclesonide, arformoterol tartrate/ciclesonide.

[0064] In another aspect, the invention provides for the use of inhaled administration of Compound I in combination with other bronchodilator drug combinations, particularly B2 agonist/M3 antagonist combinations (i.e. triple combination product), including but not limited to salmeterol xinafoate/tiotropium bromide, formoterol fumarate/tiotropium bromide, BI 1744 CL/tiotropium bromide, indacaterol/NVA237, indacaterol/QAT-370, formoterol/LAS34273, GSK159797/GSK 573719, GSK159802/GSK 573719, GSK642444/GSK 573719, GSK159797/GSK 233705, GSK159802/GSK 233705, GSK642444/GSK 233705, and compounds which possess both B2 agonist and M3 antagonist activity in the same molecule (dual functionality) such as GSK 961081.

Compound I can be in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refer to salts prepared from pharmaceutically acceptable inorganic and organic acids and bases.

[0065] Pharmaceutically acceptable inorganic bases include metallic ions. Exemplary metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like and in their usual valences. Exemplary salts include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Exemplary salts are the ammonium, calcium, magnesium, potassium, and sodium salts.

[0066] Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, including in part, trimethylamine, diethylamine, N, N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-

methylglucamine) and procaine; substituted amines including naturally occurring substituted amines; cyclic amines; quaternary ammonium cations; and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[0067] Illustrative pharmaceutically acceptable acid addition salts of the compounds of the present invention may be prepared from the following acids, including, without limitation formic, acetic, propionic, benzoic, succinic, glycolic, gluconic, lactic, maleic, malic, tartaric, citric, nitic, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, hydrochloric, hydrobromic, hydroiodic, isocitric, trifluoroacetic, pamoic, propionic, anthranilic, mesylic, oxalacetic, oleic, stearic, salicylic, p-hydroxybenzoic, nicotinic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, phosphoric, phosphonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, sulfuric, salicylic, cyclohexylaminosulfonic, algenic, β -hydroxybutyric, galactaric and galacturonic acids. Exemplary pharmaceutically acceptable salts include the salts of hydrochloric acid and trifluoroacetic acid.

[0068] All of the above salts may be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention. For example, the pharmaceutically acceptable salts of the present invention may be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts may be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are contemplated. Lists of suitable salts are found in Remington's

Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p.1418, the disclosure of which is hereby incorporated by reference.

[0069] "Prodrug" refers to a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis, reduction or oxidation) to a compound of the invention. Suitable groups for forming pro-drugs are described in 'The Practice of Medicinal Chemistry, 2nd Ed. pp561-585 (2003) and in F. J. Leinweber, Drug Metab. Res., 18, 379. (1987). It will be understood that, as used in herein, references to the compounds of the invention are meant to also include the prodrug forms.

[0070] Various polymorphs of a Compound I forming part of this invention may be prepared by crystallization of Compound I under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Heating or melting the compound followed by gradual or fast cooling may also obtain polymorphs. The presence of polymorphs may be determined by IR spectroscopy, differential scanning calorimetry, powder X-ray powder diffraction pattern or such other techniques.

[0071] Administration of Compound I by inhalation via the mouth or nose may be by powder inhalation, or by aerosol nebulizers. Aerosol generation can be carried out, for example, by pressure-driven jet atomisers or ultrasonic atomisers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

[0072] The active compound may be dosed as described depending on the inhaler system used. In addition to the active compound the administration forms may contain excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilisers, preservatives, flavourings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds as discussed above.

[0073] The amount of active ingredient utilised in inhalable formulations according to the invention is usually from about 0.01 to about 1% by weight, in some embodiments from about 0.05 to about 0.5% by weight, and in other

embodiments about 0.3% by weight, based on the total weight of the aerosol formulation. All weight percentages described herein are based on the total weight of the formulation unless stated otherwise.

[0074] Inhaled administration may take place using a range of delivery devices and formulations including, but not limited to, nebulisers, meter dose inhalers and dry powder inhalers. Since the physical characteristics of a drug product required to optimise delivery from different devices vary, the form of Compound I administered may include, but is not limited to, the free base, an aqueous soluble salt, or an aqueous insoluble salt.

[0075] In one embodiment, the Compound I is administered by direct inhalation into the respiratory system of a subject for delivery as a mist or other aerosol or dry powder. Delivery of Compound I substantially directly to the subject's lungs provides numerous advantages including providing an extensive surface area for drug absorption, direct delivery of therapeutic agents to the disease site in the case of regional drug therapy, eliminating the possibility of drug degradation in the subject's intestinal tract (a risk associated with oral administration), and eliminating the need for repeated subcutaneous injections. In the particular case of PPAR α agonists such as Compound I, which are active by the inhaled route in respiratory disease, the inhaled route offers the advantage of reduced systemic exposure, as described above, thereby minimizing unwanted side effects characteristic of this class of drug.

[0076] Aerosols of liquid particles comprising the active materials may be produced by any suitable means, such as inhalatory delivery systems. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier. The carrier is typically water, and may be sterile, pyrogen-free water, or a dilute aqueous alcoholic solution, in some embodiments isotonic, but may be hypertonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not made sterile, for example, methyl hydroxybenzoate, as well as antioxidants,

flavoring agents, volatile oils, buffering agents and surfactants, which are normally used in the preparation of pharmaceutical compositions.

[0077] Aerosols of solid particles comprising the active materials may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles, which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration.

[0078] One type of solid particulate aerosol generator contemplated as useful in conjunction with the present invention may be an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders, which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened *in situ* and the powder delivered by means of air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator either consists solely of the active ingredient or of a powder blend comprising the active materials, a suitable powder diluent, such as lactose, and an optional surfactant.

[0079] A second type of aerosol generator contemplated as useful in conjunction with the present invention may be a metered dose inhaler (MDI). Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the compound in a liquefied propellant. During use, the metered dose inhaler discharges the formulation through a valve, adapted to deliver a metered volume, to produce a fine particle spray containing the active materials. Any propellant may be used for aerosol delivery, including both chlorofluorocarbon-containing propellants and non-chlorofluorocarbon-containing propellants. Propellants suitable for use are known to the skilled person, and include CFC-12, HFA-134a, HFA-227, HCFC-22 (CCl₂F₂) and HFA-152 (C₂H₄F₂) and isobutane.

[0080] A third type of aerosol generator contemplated as useful in conjunction with the present invention may be an electrohydrodynamic (EHD)

aerosol generating device, which has the advantage of being adjustable to create substantially monomodal aerosols having particles more uniform in size than aerosols generated by other devices or methods. Typical EHD devices include a spray nozzle in fluid communication with a source of liquid to be aerosolized, at least one discharge electrode, a first voltage source for maintaining the spray nozzle at a negative (or positive) potential relative to the potential of the discharge electrode, and a second voltage source for maintaining the discharge electrode at a positive (or negative) potential relative to the potential of the spray nozzle. Most EHD devices create aerosols by causing a liquid to form droplets that enter a region of high electric field strength. The electric field then imparts a net electric charge to these droplets, and this net electric charge tends to remain on the surface of the droplet. The repelling force of the charge on the surface of the droplet balances against the surface tension of the liquid in the droplet, thereby causing the droplet to form a cone-like structure known as a Taylor Cone. In the tip of this cone-like structure, the electric force exerted on the surface of the droplet overcomes the surface tension of the liquid, thereby generating a stream of liquid that disperses into a many smaller droplets of roughly the same size. These smaller droplets form a mist, which constitutes the aerosol cloud that the user ultimately inhales.

[0081] In a particular embodiment of the invention, a composition of the invention is in dry powder form, for delivery using a dry powder inhaler (DPI). Many types of DPI are known. Microparticles for delivery by administration may be formulated with excipients that aid delivery and release. For example, in a dry powder formulation, microparticles may be formulated with large carrier particles that aid flow from the DPI into the lung. Suitable carrier particles are known, and include lactose particles; they may have a mass median aerodynamic diameter of greater than 90 μm .

[0082] For the purposes of inhalation, a large number of apparatus are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is appropriate for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the

case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhalers for example as described in European Patent Application EP 0 505 321).

[0083] In determining the effective amount or dose of Compound I, a number of factors are considered by the attending diagnostician, including, but not limited to, the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

[0084] As used herein, the terms "therapeutically effective" are intended to qualify the amount of an agent for use in therapy that will achieve the goal of preventing, or improvement in the severity of, the disorder being treated, while avoiding adverse side effects typically associated with alternative therapies. A respiratory disorder symptom is considered ameliorated or improved if any benefit is achieved, no matter how slight.

[0085] It will be appreciated that the amount of Compound I required for use in the treatment or prevention of a respiratory disorder will vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage is described herein, although the limits that are identified as being exemplary may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages. Once or twice daily dosing by inhalation is contemplated.

[0086] The appropriate dosage level of Compound I will generally be from about 0.1 µg to about 50 mg per day, which may be administered in single or multiple doses. In exemplary embodiments, the dosage level will be about 1 µg to about 10 mg per day; In other embodiments, about 10 µg to about 2 mg per day. Once or twice daily dosing by inhalation is contemplated.

[0087] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's *The Pharmacological Basis of Therapeutics*, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[0088] The effectiveness of a given dosage or the effectiveness of the treatment may be assayed, in accordance with the invention, by any technique capable of assessing inflammation. In a one embodiment, the

treatment of the respiratory disease is assessed by counting cells recovered by bronchoalveolar lavage (BAL). Inflammation can also be assessed in sputum or in bronchial epithelial biopsies.

[0089] Advantageously, the cells may be selected from one or more of macrophages, epithelial cells, neutrophils, eosinophils and lymphocytes.

[0090] The invention is capable of substantially reducing inflammation in respiratory diseases. Advantageously the neutrophil count recovered by BAL may be reduced by 50% or more upon administration of Compound I, in some embodiments, 60% or more.

[0091] An "effective dose" of the compounds of the present invention also refers to monitoring the treatment of inflammatory conditions and/or respiratory disease in a subject by obtaining a response in an assay which measures inflammation in respiratory disease. The assay may be a bronchoalveolar lavage (BAL) followed by cell counting, wherein then presence of cells indicates inflammation of the lung. In human patients, BAL, induced sputum and bronchial biopsy are exemplary methods of assessing inflammation. Inflammation may be induced by any desired means, such as tobacco smoke inhalation. Tobacco smoke inhalation is preferred since it reproduces an inflammatory response that is resistant to oral or inhaled steroids as is seen in COPD (Medicherla *et al*, J Pharmacol Exp Ther. 2008 Mar;324(3):921-9). In the context of the BAL/cell counting assay, "effective" encompasses a reduction in neutrophil numbers by 50% or more compared to a control in which the agent is not administered.

[0092] In addition, the effectiveness of a particular dosage of Compound I, alone or in combination with a respiratory treatment agent, may be assessed by monitoring the effect of a given dosage on the progress or prevention of a particular respiratory disorder. COPD is not easy to diagnose in its beginning stages. Because early COPD may produce no visible symptoms or signs (which is why a simple medical history and physical examination by a doctor may fail to find it), laboratory tests must be used to detect the presence of airflow obstruction. A lab test called "spirometry" measures the volume of air that a subject expels from their lungs after they have taken in a deep breath. The full volume of that expelled air is called FVC (Forced Vital Capacity) and the volume of air expelled in the first second is called the FEV1.0 (Forced

Expiratory Volume 1 Second). An abnormally low FEV1.0/FVC means that the airflow is obstructed. If someone has COPD, a low FEV1.0 not only reveals that the person has obstructive lung disease, but can measure how severe the obstruction is.

[0093] In an exemplary embodiment, the present invention encompasses the prevention or treatment of respiratory disorders. In some embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the respiratory disorders selected from the group consisting of asthma (mild, moderate or severe), steroid resistant asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary edema, pulmonary embolism, pneumonia, pulmonary sarcoisosis, silicosis, pulmonary fibrosis, respiratory failure, acute respiratory distress syndrome, emphysema, chronic bronchitis, tuberculosis, and lung cancer. In particular, the methods and compositions of the present invention may encompass the prevention and treatment of the respiratory disorder, COPD.

[0094] As used herein, the term "chronic obstructive pulmonary disease" or "COPD" refers to a set of physiological symptoms including chronic bronchitis, chronic cough, expectoration, exertional dyspnea and a significant, progressive reduction in airflow that may or may not be partly reversible. Emphysema may also be present in the lungs. COPD is a disease characterized by a progressive airflow limitation caused by an abnormal inflammatory reaction to the chronic inhalation of particles.

[0095] In subjects with the disorder, poor gas exchange in the lungs leads to decreased oxygen levels in the blood, increased levels of carbon dioxide and shortness of breath. Chronic airflow obstruction in COPD is complicated by the loss of lung elasticity resulting from enzymatic destruction of the lung parenchyma. Rather than a single pathologic condition, COPD is an umbrella term encompassing chronic obstructive bronchitis and emphysema.

[0096] Compound I has been found to be existing in at least three different crystalline forms, including two novel polymorphs, which are Form 0, Form I and Form II herein. As mentioned above, Form 0 is the form obtained by the method of Example 6 of International application WO98/45292 (US patent no. 6,011,036). Forms I and II are novel forms identified by the present inventors. Comparison of the XRPD patterns and FT-IR spectra of Form 0 (Figs 9 and

10), Form I (Figs 4 and 5) and Form II (Figs 7 and 8) confirms the distinct identities of the three forms. Examples below describe the preparation of the novel Forms I and II and the data associated therewith. Form II is much more stable than Form I towards process-induced physical (polymorphic) changes following micronization (particle size reduction in both dry and wet methods) to produce the active ingredient suitable for inhalation. Form I, can be stabilized towards process-induced transformations using stabilizers and/or strategies known through prior art. Also, mixtures of various Forms can also exist mentioned in this invention and provide desired results anticipated by each of the polymorphs.

[0097] Hence one embodiment of the present invention provides Form II of Compound I characterized by having an X-ray powder diffraction pattern comprising a peak intensity expressed in degrees 2θ of 15.54 ± 0.1 , and further characterized by peak intensities that are selected from the group consisting of 6.06 ± 0.1 , 8.50 ± 0.1 , 12.20 ± 0.1 , 13.78 ± 0.1 , 17.52 ± 0.1 , 21.32 ± 0.1 , 21.80 ± 0.1 , 23.54 ± 0.1 and 26.34 ± 0.1 . Form II is further characterized by a single melting endotherm peak between about 168°C and 178°C as measured by differential scanning calorimetry.

[0098] In exemplary embodiments, the crystalline Form II of Compound I is characterised by having an X-ray powder diffraction pattern substantially in accordance with that shown in Fig. 7.

[0099] The crystalline Form II is anhydrous, and substantially non-hygroscopic.

[00100] In the use, method of treatment, composition and kit aspects of the invention described above, Compound I may be the Form II polymorph.

[00101] The present invention also includes a novel crystalline Form I of Compound I characterized by having an X-ray powder diffraction pattern comprising a peak intensity expressed in degrees 2θ of 15.60 ± 0.1 , and further characterized by peak intensities that are selected from the group consisting of 9.78 ± 0.1 , 11.94 ± 0.1 , 12.70 ± 0.1 , 14.00 ± 0.1 , 14.88 ± 0.1 , 15.60 ± 0.1 , 21.82 ± 0.1 and 24.28 ± 0.1 . Form I is further characterized by two melting peaks, which are an exotherm between about 111°C and 125°C and an endotherm between 168°C and 178°C , as measured by differential scanning calorimetry.

[00102] In exemplary embodiments, the crystalline Form I of Compound I is characterised by having an X-ray powder diffraction pattern substantially in accordance with that shown in Fig. 4.

[00103] The following examples describe embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered exemplary only, with the scope and spirit of the invention being indicated by the claims, which follow the examples. In the examples, all percentages are given on a weight basis unless otherwise indicated.

EXAMPLE 1

Pre-clinical mouse model of COPD inflammation – Tobacco smoke induced pulmonary inflammation.

[00104] Previous studies established that the number of neutrophils recovered in the bronchoalveolar lavage (BAL) is significantly elevated 24 hours following the final Tobacco Smoke (TS) exposure of 4 or 11 consecutive daily TS exposures, this time point was used in the present study.

[00105] Protocols for the exposure of mice to TS, obtaining bronchoalveolar lavage (BAL), preparation of cytospin slides for differential cell counts are as outlined below.

Exposure of mice to TS daily for 4 or 11 consecutive days

[00106] In this exposure protocol, mice were exposed in groups of 5 in individual clear polycarbonate chambers (27 cm x 16 cm x 12 cm). The TS from the cigarettes was allowed to enter the exposure chambers at a flow rate of 100 mL/min. In order to minimize any potential problems caused by repeated exposure to a high level of TS (6 cigarettes), the exposure of the mice to TS was increased gradually over the exposure period to a maximum of 6 cigarettes. The exposure schedule used for 4 days was as follows:

Day 1: 4 cigarettes	(approximately 32 min exposure)
Day 2: 4 cigarettes	(approximately 32 min exposure)
Day 3: 6 cigarettes	(approximately 48 min exposure)
Day 4: 6 cigarettes	(approximately 48 min exposure)

[00107] The exposure schedule used for 11 days exposure was as follows:

Day 1: 2 cigarettes	(approximately 16 min exposure)
Day 2: 3 cigarettes	(approximately 24 min exposure)
Day 3: 4 cigarettes	(approximately 32 min exposure)
Day 4: 5 cigarettes	(approximately 40 min exposure)
Day 5 to 11: 6 cigarettes	(approximately 48 min exposure)

[00108] A further group of mice was exposed to air on a daily basis for equivalent lengths of time as controls (no TS exposure).

Bronchoalveolar lavage (BAL) analysis

[00109] Bronchoalveolar lavage was performed as follows: the trachea was cannulated using a Portex nylon intravenous cannula (pink luer fitting) shortened to approximately 8 mm. Phosphate buffered saline (PBS) was used as the lavage fluid. A volume of 0.4 mL was gently instilled and withdrawn 3 times using a 1 mL syringe and then placed in an Eppendorf tube and kept on ice prior to subsequent determinations.

Cell counts:

[00110] Lavage fluid was separated from cells by centrifugation and the supernatant decanted and frozen for subsequent analysis. The cell pellet was re-suspended in a known volume of PBS and total cell numbers calculated by counting a stained (Turks stain) aliquot under a microscope using a haemocytometer.

Differential cell counts were performed as follows:

[00111] The residual cell pellet was diluted to approximately 10^5 cells per mL. A volume of 500 μ L was placed in the funnel of a cytopsin slide and centrifuged for 8 min at 800 rpm. The slide was air dried and stained using 'Kwik-Diff' solutions (Shandon) as per the proprietary instructions. When dried and cover-slipped, differential cells were counted using light microscopy. Up to 400 cells were counted by unbiased operator using light microscopy. Cells were differentiated using standard morphometric techniques.

Drug Treatment

[00112] Rodents such as mice and rats are obligate nasal breathers thus oral delivery of test materials (such as therapeutic agents) for inhalation will not produce good lung exposure. As a consequence, delivery of therapeutic agents to the lungs in rodents is generally achieved by intra-nasal, intra-tracheal or inhalation by whole body aerosol exposure in a chamber.

[00113] The chamber method utilises large amounts of test material and is generally reserved for inhalation toxicology studies rather than pharmacological efficacy studies. Intra-tracheal administration is a very efficient delivery method as almost all of the test material is delivered to the lungs, but this is quite an invasive technique. For studies in the mouse particularly, it is also quite technically demanding as the diameter of the trachea is quite small. The intranasal route is less invasive than the intra-tracheal route and so is particularly suitable for repeat dosing studies such as the 4-11 day mouse model described below. Following intranasal administration ~50% of the dose administered is delivered to the lungs (Eyles JE, Williamson ED and Alpar HO. 1999, Int J Pharm, 189(1):75-9).

[00114] For the intra-nasal dose studies (as a surrogate for oral inhalation), mice were dosed intra-nasally with vehicle (0.2% tween 80 in saline), Compound I (0.1 mg/kg), Rosiglitazone (0.1 mg/kg), Compound II (0.1 mg/kg), or Farglitazar (0.1 mg/kg) at 1 hour prior to tobacco smoke exposure each day. Compound 1 was used in its Form 0. The control group of mice received vehicle 1 hour prior to being exposed to air daily for a maximum of 50 minutes per day. BAL was performed 24 hours following the final TS exposure.

[00115] For the oral dose studies, mice were dosed orally with vehicle (0.75% carboxymethyl cellulose in water), Rosiglitazone (5 mg/kg), Compound II (5 mg/kg), or Farglitazar (5 mg/kg) at 1 hour prior to TS exposure each day. The control group of mice received vehicle 1 hour prior to being exposed to air daily for a maximum of 50 minutes per day. BAL was performed 24 h following the final TS exposure.

Data management and statistical analysis

[00116] All results are presented as individual data points for each animal and the mean value was calculated for each group. Since tests for normality were positive the data was subjected to a one way analysis of variance test (ANOVA), followed by a Bonferroni correction for multiple comparisons in order to test for significance between treatment groups. A "p" value of < 0.05 was considered to be statistically significant. Percentage inhibitions were automatically calculated within the Excel spreadsheets for the cell data using the formula below:

$$\% \text{ Inhibition} = 1 - \left(\frac{\text{Treatment group result} - \text{sham group result}}{\text{TS vehicle group result} - \text{sham group result}} \right) \times 100$$

[00117] Inhibition data for other parameters were calculated manually using the above formula.

[00118] As illustrated in Figure 1, both Rosiglitazone and Compound I when administered by a surrogate route for inhalation (0.1 mg/kg intranasally) inhibit TS induced BAL influx of neutrophils. In contrast, both Farglitazar and Compound II are ineffective when administered in similar fashion. This lack of pulmonary anti-inflammatory activity was confirmed when the PPAR gamma agonists were administered by the oral route. At doses effective by this route in mouse diabetes models (5 mg/kg) both Farglitazar and Compound II were ineffective. In contrast, Rosiglitazone significantly inhibited BAL neutrophil influx when administered in a similar fashion.

EXAMPLE 2

Evidence for activity of Compound II and Farglitazar in mouse diabetes models.

[00119] In previous studies, both Compound II and Farglitazar have been shown to be efficacious in mouse diabetes models at or below 5 mg/kg when dosed orally. For Farglitazar see Henke et al, J Med Chem, 1998, 41(25):5020-36.

For Compound II see Chakrabarti et al, Diabetes, Obesity and Metabolism, 2002, 4:319-328.

EXAMPLE 3

Superior suitability of Compound I compared with Rosiglitazone for the treatment of lung diseases such as COPD when administered by the inhaled route

[00120] The plasma clearance and oral bioavailability of Compound I in male wistar rats was examined by standard in vivo pharmacokinetic studies known in the art. A single dose of 5 mg/kg of Compound I (micronised Form II) was administered in polysorbate 80 vehicle by oral gavage and plasma samples taken 30 minutes, 1 hour, 2 hours, 3 hours, 5 hours, 8 hours, 10 hours and 24 hours. A single 1 mg/kg dose of Compound I was administered in 5% dimethyl sulphoxide; 20% hydroxy propyl- β -cyclodextrine by the intravenous (IV) route and plasma samples taken 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 5 hours and 8 hours. Concentrations of Compound I in the various plasma samples were determined using standard analytical procedures.

[00121] Standard pharmacokinetic parameters following IV or oral dosing were calculated from the plasma concentration data, including Area under the curve (AUC), maximum plasma concentration (C_{max}), time of maximum plasma concentration (T_{max}), Elimination time (K_{el}), plasma half-life ($T_{1/2}$), Volume of distribution (V_d), plasma clearance (Cl) and oral bioavailability.

[00122] Compound I was also examined in male beagle dogs where a single 1 mg/kg dose was administered in 5% dimethyl sulphoxide; 20% hydroxy propyl- β -cyclodextrine and plasma samples taken 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 5 hours, 8 hours and 10 hours. Concentrations of Compound I in the various plasma samples were determined using standard analytical procedures.

[00123] Standard pharmacokinetic parameters following IV dosing were calculated from the plasma concentration data, including Area under the curve (AUC), maximum plasma concentration (C_0), Elimination time (K_{el}), plasma half-life ($T_{1/2}$), Volume of distribution (V_d) and plasma clearance (Cl).

	Form II of Compound I	Rosiglitazone Maleate*
Oral bioavailability	48% (rat)	100% (rat), 99% (human)
Plasma clearance (IV route) (ml/hr/kg)	370 (rat), 300 (dog)	50-81 (rat), 127 (dog)
Melting point	172-178°C	122-123°C

*Data from Avandia FDA Pharmacology review (http://www.fda.gov/cder/foi/nda/99/21071_Avandia.htm) and Muzeeb *et al*, Xenobiotica. 2006, 36(9):838-56.

[00124] Compound I has lower oral bioavailability and faster systemic clearance than Rosiglitazone reducing the likelihood of systemic activity following inhalation.

EXAMPLE 4

Preparation of crystalline Form I of 5-{4-[2-(4-methyl-1-oxo-1H-phthalazin-2-yl)-ethoxy] benzyl} thiazolidine-2,4-dione

[00125] 5-{4-[2-(4-Methyl-1-oxo-1H-phthalazin-2-yl)-ethoxy] benzyl} thiazolidine-2,4-dione (20 gram) prepared by the process described in US patent no. US 6,011,036, or by any other process, is suspended in 80 ml of methanol and heated under reflux for a period of 2 to 3 hours and the reaction mass is cooled to 10 °C to 15 °C. The product is subsequently isolated by filtration, washed with 20 mL of chilled methanol (10 °C to 15 °C), and dried at 50-60 °C for 4-5 hours. The compound is obtained as Form I as white to off-white crystals (weight 14.5 grams).

[00126] ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.97 (bs, 1H, D₂O exchangeable), 8.29 (d, *J* = 8.0 Hz, 1H), 7.95-7.90 (m, 2H), 7.89-7.85 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.84 (dd, *J* = 4.4 Hz, 1H), 4.46 (t, *J* = 6.0 Hz, 2H), 4.35 (t, *J* = 6.0 Hz, 2H), 3.30-3.26 (m, 1H), 3.05-2.99 (m, 1H), 2.50 (s, 3H).

[00127] HPLC 99.18% [column: Symmetry shield RP-18 (150 mm x 4.6 mm), 5 μ m; mobile phase: 10 mM KH_2PO_4 (pH 3.0 using H_3PO_4) / CH_3CN (40:60); flow rate: 1.0 mL/min; UV detection at 210 nm; RT 14.24 min.].

EXAMPLE 5

Preparation of crystalline Form II of 5-{4-[2-(4-methyl-1-oxo-1*H*-phthalazin-2-yl)-ethoxy] benzyl} thiazolidine-2,4-dione

[00128] 5-{4-[2-(4-Methyl-1-oxo-1*H*-phthalazin-2-yl)-ethoxy] benzyl} thiazolidine-2,4-dione (20 gram) prepared by the process described in US patent no. US 6,011,036, or by any other process, is suspended in 100 ml of acetone and heated under reflux for period of 5-6 hours and the reaction mass is cooled to 10-15 °C. The product is subsequently isolated by filtration, washed with 40 mL of chilled acetone (10 °C to 15 °C), and dried at 60 °C to 70 °C for 12 hours to 15 hours. The compound is obtained as Form II as white to off-white crystals (weight 16 grams).

[00129] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.97 (bs, 1H, D_2O exchangeable), 8.29 (d, $J = 8.0$ Hz, 1H), 7.95-7.90 (m, 2H), 7.89-7.85 (m, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 4.84 (dd, $J = 4.4$ Hz, 1H), 4.46 (t, $J = 6.0$ Hz, 2H), 4.35 (t, $J = 6.0$ Hz, 2H), 3.30-3.26 (m, 1H), 3.05-2.99 (m, 1H), 2.50 (s, 3H).

[00130] HPLC 99.18% [column: Symmetry shield RP-18 (150 mm x 4.6 mm), 5 μ m; mobile phase: 10 mM KH_2PO_4 (pH 3.0 using H_3PO_4) / CH_3CN (40:60); flow rate: 1.0 mL/min; UV detection at 210 nm; RT 14.24 min.].

Characterization of Form I and Form II of Compound I:

[00131] Form I and Form II are characterized by Differential Scanning Calorimetry (DSC), X-ray powder diffraction pattern (XRPD) and Fourier Transform Infra Red (FTIR) spectroscopic techniques.

Differential Scanning Calorimetry (DSC) and Thermal Analysis:

[00132] DSC analysis was performed using a Q₂₀₀₀ DSC (TA instrument, USA). The samples (3-5 mg) were analysed under dry nitrogen purge (50 mL/min) in aluminium T-Zero pans at a heating rate of 3 °C. The temperature

of the melting endothermic peak was reported as the melting point. The data from DSC analyses was dependent on several factors, including the rate of heating, the purity of the sample, crystal size, and sample size. Form II of Compound I is characterized by a single melting endotherm peak at a temperature between about 168 °C and 178 °C, or between about 172 °C and 176 °C, particularly about 174 °C as measured by DSC. Form I of Compound I is characterized by two peaks, which include, an exotherm between about 111 °C and 125 °C and an endotherm between 168 °C and 178 °C, as measured by DSC.

[00133] Form I & II recorded negligible weight loss (< 0.2% w/w) up to 150 °C as analyzed using Thermo-gravimetric analyzer (Q₅₀₀₀ IR, TA Instrument, USA). Form I and II also showed very less propensity to adsorb moisture (< 3% w/w for Form I and < 1% w/w for Form II at 90% RH at 25°C) as recorded using sorption analyzer (Q₅₀₀₀ SA, TA Instrument, USA). These experiments corroborate the findings that both Form I and Form II can be termed as non-hygroscopic.

X-Ray Powder Diffraction (XRPD):

[00134] The crystal structures of Forms I and II of compound I were analyzed using X-ray powder diffraction ("XRPD"). The X-ray powder diffraction spectra were determined using a Rigaku D/Maz 2200 diffractometer equipped with horizontal goniometer in $\theta/2\theta$ geometry. The X-ray tube used was a Cu K-alpha with a wavelength of 1.5418 Å at 50 KV and 34 mA. The divergence and scattering slits were set at 0.5° and the receiving slit set at 0.15 mm. Diffracted radiation was detected by scintillation counter detection, θ to 2θ continuous scan at 3 degrees/minute from 3 to 45 degrees.

[00135] An illustrative XRPD pattern for crystalline Form I is shown in Fig 4. and for crystalline Form II is shown in Fig 7. Table 1 & Table 2 list the corresponding main diffraction peaks in terms of 2θ values and intensities for crystalline 5-{4-[2-(4-methyl-1-oxo-1*H*-phthalazin-2-yl)-ethoxy] benzyl} thiazolidine-2,4-dione for Form I and Form II respectively.

Table-1: XRPD data of Form I

<u>2 Theta (2θ)</u>	<u>Percentage relative intensity (I/I₀)</u>
9.78	19
11.94	52
12.70	62
14.00	22
14.88	40
15.60	100
21.82	32
24.28	20

Table-2: XRPD data of Form II

<u>2 Theta (2θ)</u>	<u>Percentage relative intensity (I/I₀)</u>
6.06	28
8.50	46
12.20	39
13.78	76
15.54	100
17.52	19
21.32	26
21.80	19
23.54	25
26.34	49

Fourier-Transform Infrared (FT-IR) Spectrometry:

[00136] Form I and Form II of Compound I were also characterized by Fourier Transform Infra Red (FT-IR) spectra and recorded in solid state as KBr dispersion. A Shimadzu IR Prestige21 Fourier Transform Infra Red spectrophotometer was used for characterization. Experimental error, unless otherwise noted, was $\pm 2 \text{ cm}^{-1}$.

[00137] Form I of 5-{4-[2-(4-methyl-1-oxo-1*H*-phthalazin-2-yl)-ethoxy]benzyl} thiazolidine-2,4-dione was shown to have infrared spectrum comprising absorption bands at about 3122, 2966, 2771, 1751, 1703, 1649, 1629, 1612, 1583, 1512, 1485, 1462, 1436, 1415, 1388, 1371, 1348, 1328, 1301, 1271, 1251 cm^{-1} . The infrared spectrum is substantially in accordance with that shown in Fig. 7.

[00138] Form II of 5-{4-[2-(4-methyl-1-oxo-1*H*-phthalazin-2-yl)-ethoxy]benzyl} thiazolidine-2,4-dione was shown to have infrared spectrum comprising absorption bands at about 3161, 3061, 2954, 2922, 2883, 2748, 1759, 1741, 1707, 1651, 1614, 1589, 1514, 1481, 1440, 1406, 1369, 1334, 1303, 1242 cm⁻¹. The infrared spectrum is substantially in accordance with that shown in Fig. 8.

Stability of Form I & II of Compound I under accelerated conditions of storage

[00139] Form I & II were found to be chemically stable under accelerated conditions of storage at 60°C and 40°C/75% RH for 1 month. Moreover, no significant weight increase was recorded after 1 month storage under accelerated conditions for both Form I & II.

EXAMPLE 6

Clinical trial to demonstrate anti-inflammatory activity of Compound I administered by inhalation to COPD patients.

[00140] Patients suffering from COPD are first put through a run-in period and are then split into 2 groups of approximately equal numbers. Each group is then given Compound or placebo for a period of 4-12 weeks. Sputum and bronchial biopsies are taken at baseline and post 4, 8 and 12 weeks treatment, dependent on the duration of the study. Inflammatory cells and mediators are quantified in the sputum and bronchial biopsy samples. The primary efficacy variables are sputum neutrophil counts (total and percentage counts) and lung function determined by spirometry (FEV1 (forced expiratory volume in one second), FVC (forced expiratory vital capacity), peak expiratory flow (PEF)), with other readouts of pulmonary inflammation as secondary efficacy variables.

EXAMPLE 7

Clinical trial to demonstrate the clinical benefit of Compound I administered by inhalation to COPD patients.

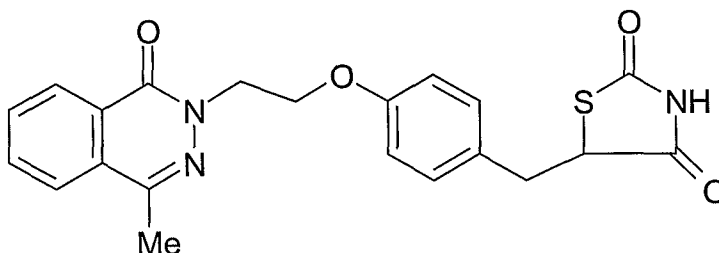
[00141] Patients suffering from COPD are first put through a run-in period and are then split into 3 groups of approximately equal numbers. Each group is then given Compound I (higher dose), Compound I (lower dose) or placebo for a period of 12-36 months.

[00142] The following parameters for each patient are monitored throughout: exacerbations (frequency and severity), FEV1 (forced expiratory volume in one second), FVC (forced expiratory vital capacity), peak expiratory flow (PEF), symptom scores and Quality of Life. Of these, exacerbation severity and frequency are considered to be primary efficacy variables, whereas the remaining parameters are considered to be secondary variables.

[00143] Although exemplary embodiments of the invention have been described using specific terms, devices, and methods, such description is for illustrative purposes only. The words used are words of description rather than of limitation. It is to be understood that changes and variations may be made by those of ordinary skill in the art without departing from the spirit or scope of the present invention, which is set forth in the following claims. In addition, it should be understood that aspects of the various embodiments may be exchanged both in whole or in part.

We claim:

1. Use of Compound I in the manufacture of a composition adapted for administration by inhalation via the mouth or nose for treatment of a respiratory disorder, wherein Compound I has the structure:



or its pharmaceutically acceptable salt thereof and/or one or more of polymorphs thereof.

2. Use according to claim 1, wherein the respiratory disorder is selected from the group consisting of asthma, steroid resistant asthma, COPD, cystic fibrosis and pulmonary fibrosis.

3. Use according to claim 1 or claim 2, wherein the administered dose of Compound I by inhalation is from about 0.1 µg to about 50 mg/day.

4. Use according to any of the preceding claims, wherein Compound I is administered in combination with a bronchodilator drug and/or another anti-inflammatory drug.

5. A method of preventing and/or treating a respiratory disorder in a subject comprising administering an amount, effective to treat such disorder, of Compound I as defined in claim 1 to the subject by inhalation via the mouth or nose.

6. The method according to claim 5, wherein the subject suffers from or is predisposed to a respiratory disorder selected from the group consisting of asthma, steroid resistant asthma, COPD, cystic fibrosis and pulmonary fibrosis.

7. The method as claimed in claim 5 or claim 6 wherein the subject is additionally administered an amount of a bronchodilator drug and/or another anti-inflammatory drug wherein the amount of Compound I and the amount of the conventional respiratory treatment agent together comprises a therapeutically effective amount.
8. A pharmaceutical composition for preventing and treating respiratory disorders in a subject, the pharmaceutical composition being adapted for inhalation via the mouth or nose and comprising Compound I as defined in claim 1 and one or more pharmaceutically acceptable carriers and/or excipients.
9. A pharmaceutical composition as claimed in claim 8 which additionally comprises a bronchodilator drug and/or another anti-inflammatory drug.
10. A kit for preventing and treating respiratory disorders in a subject, the kit comprising one dosage form comprising Compound I as defined in claim 1 and a second dosage form comprising a conventional respiratory treatment agent.
11. A crystalline Form II of Compound I as defined in claim 1, that is characterized by having an X-ray powder diffraction pattern (XRPD) comprising one or more peak intensities expressed in degrees 2θ that are selected from the group consisting of 6.06 ± 0.1 , 8.50 ± 0.1 , 12.20 ± 0.1 , 13.78 ± 0.1 , 15.54 ± 0.1 , 17.52 ± 0.1 , 21.32 ± 0.1 , 21.80 ± 0.1 , 23.54 ± 0.1 and 26.34 ± 0.1 .
12. The crystalline Form II according to claim 11, characterized by a single melting endotherm peak between about 168°C and 178°C as measured by differential scanning calorimetry (DSC).
13. The crystalline Form II according to claim 11 or claim 12, which is anhydrous.

14. The crystalline Form II according to any one of claims 11 to 13, having an X-ray powder diffraction peak at 15.54 ± 0.1 degrees 2θ .
15. The crystalline Form II according to claim 14, further having at least one additional X-ray powder diffraction peak selected from the group consisting of 6.06 ± 0.1 , 8.50 ± 0.1 , 12.20 ± 0.1 , 13.78 ± 0.1 , 21.32 ± 0.1 , 21.80 ± 0.1 , 23.54 ± 0.1 and 26.34 ± 0.1 degrees 2θ .
16. The crystalline Form II according to claim 15, further having an Fourier Transform Infra Red (FT-IR) spectrum that comprises at least one absorption band selected from the group consisting of 3161, 3061, 2954, 2922, 2883, 2748, 1759, 1741, 1707, 1651, 1614, 1589, 1514, 1481, 1440, 1406, 1369, 1334, 1303, 1242 cm^{-1} .
17. The crystalline Form II according to claim 16, further having an FT-IR spectrum that comprises at least one absorption band selected from the group consisting of 3161, 3061, 1759, 1651, 1589, 1741, 1707, 1514, 1334 and 1242 cm^{-1} .
18. The pharmaceutical composition as claimed in claim 8 in the form of a powder which is inhalable via the mouth for pulmonary delivery, wherein Compound I is in crystalline Form II as defined in any one of claims 11 to 17.
19. The crystalline Form II according to claim 11, has XRPD as shown in Fig. 7.
20. The crystalline Form II according to claim 12, has DSC as shown in Fig. 6.
21. The crystalline Form II according to claim 16, has FT-IR as shown in Fig. 8.
22. The crystalline Form II according to claims 16 and 17, has absorption band variations in the range of about $\pm 2 \text{ cm}^{-1}$.

FIG. 1:

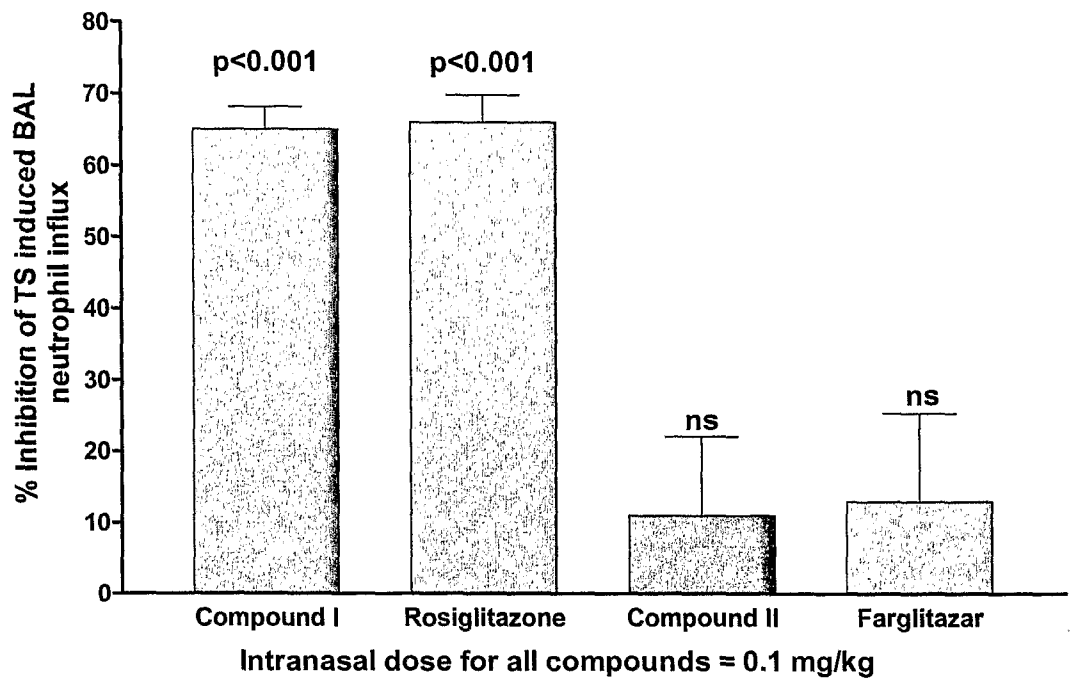


FIG. 2:

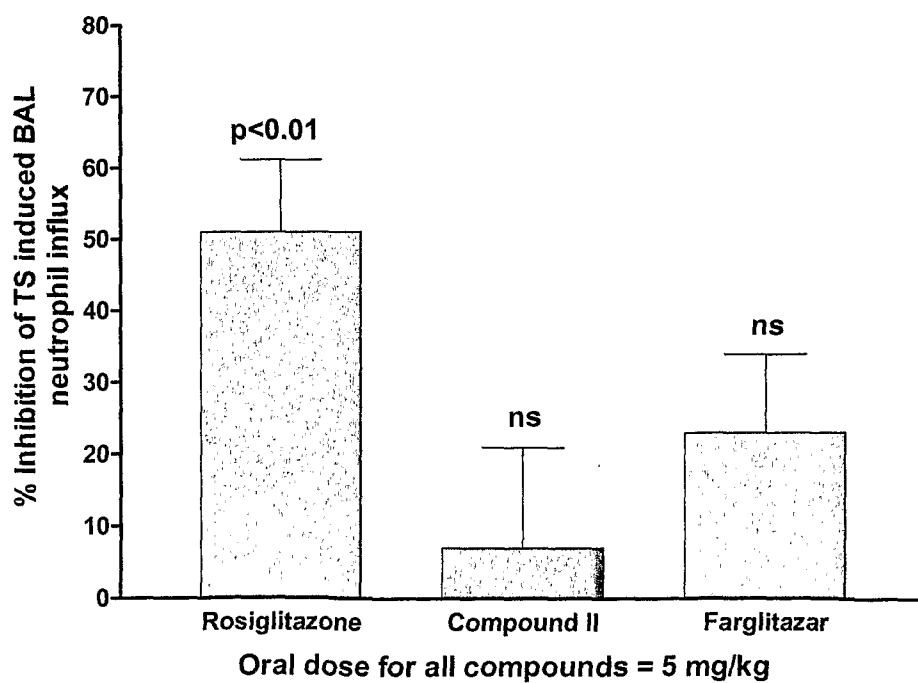


FIG. 3: DSC thermogram for Form I of Compound I

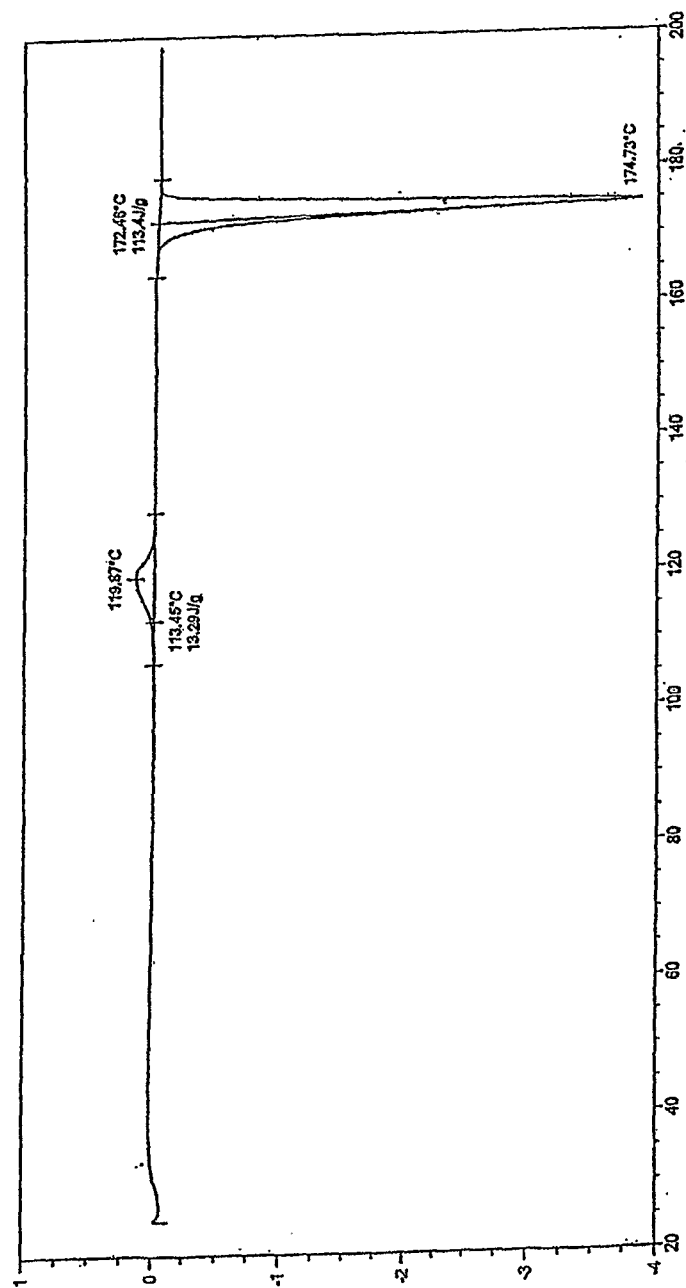


FIG. 4: X-ray powder diffraction pattern (XRPD) for Form I of Compound I

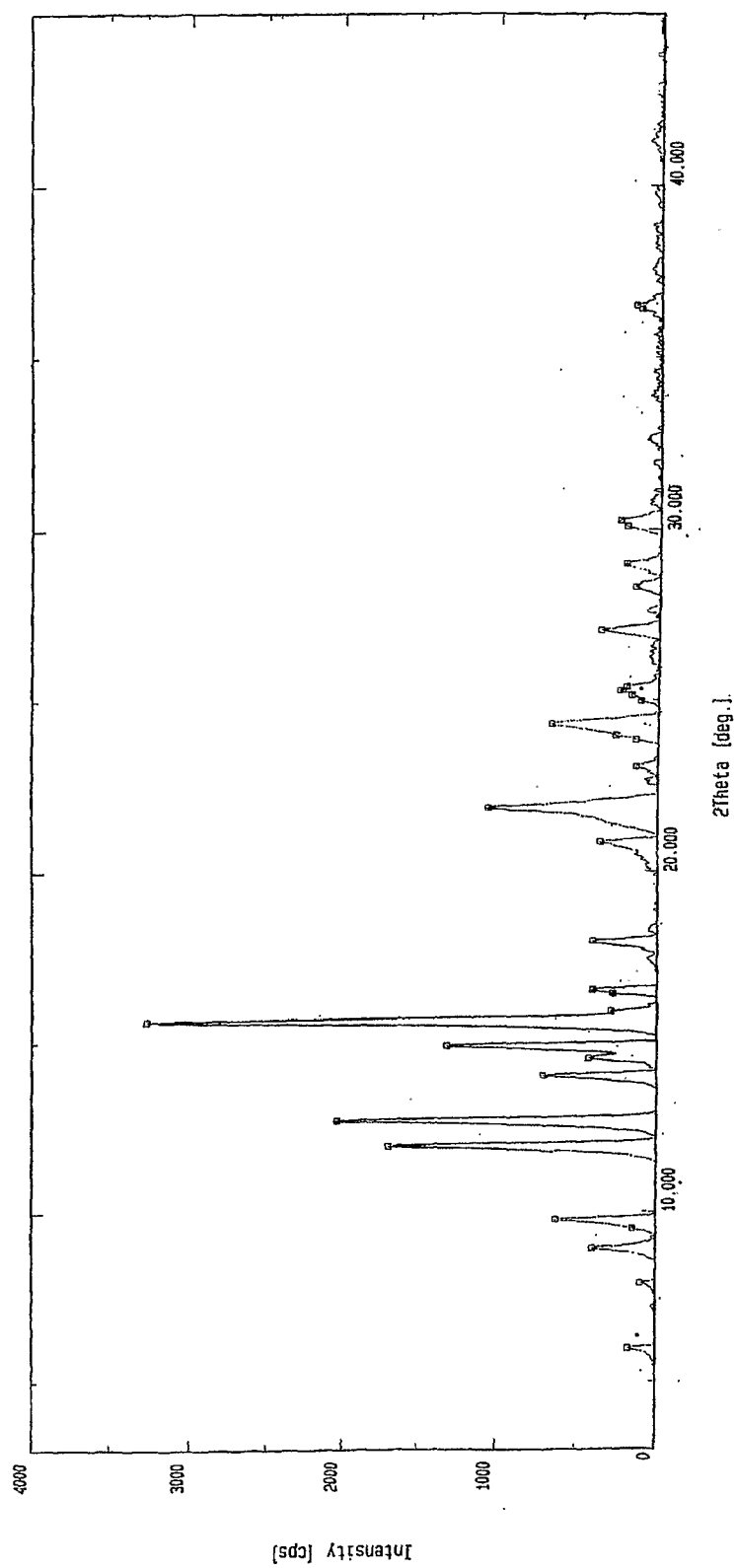


FIG. 5: Fourier Transform Infra Red (FTIR) spectrum for Form I of Compound I

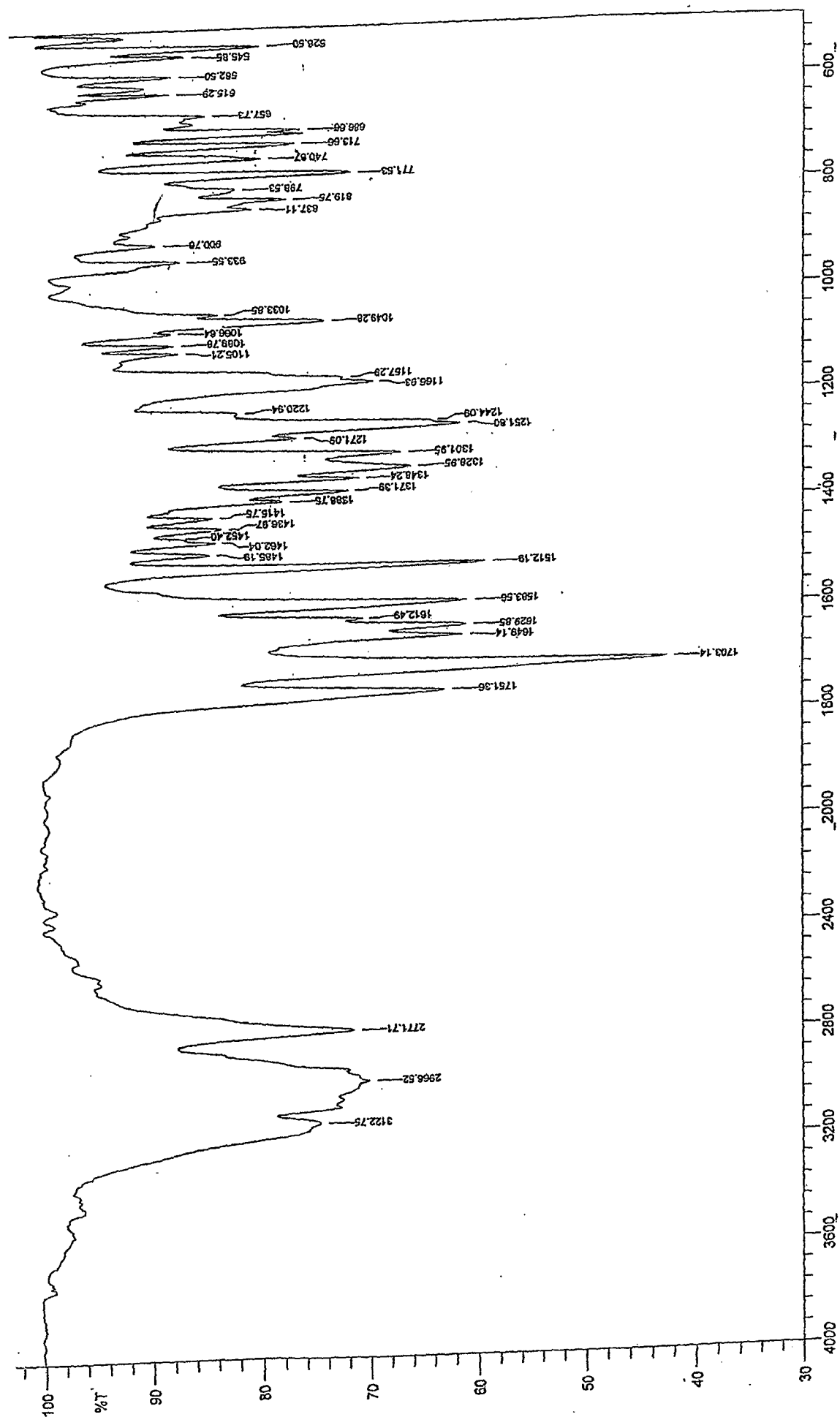


FIG. 6: DSC thermogram for Form II of Compound I

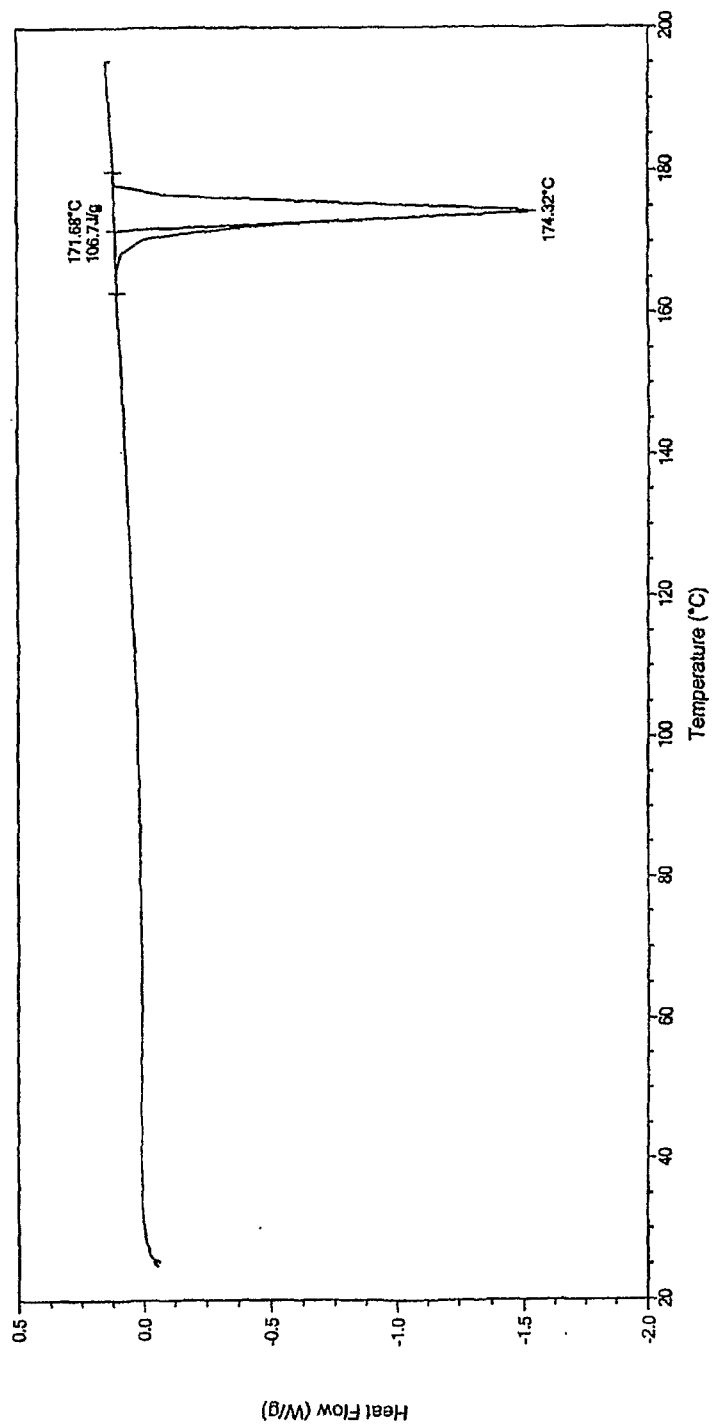


FIG. 7: X-ray powder diffraction pattern (XRPD) for Form II of Compound I

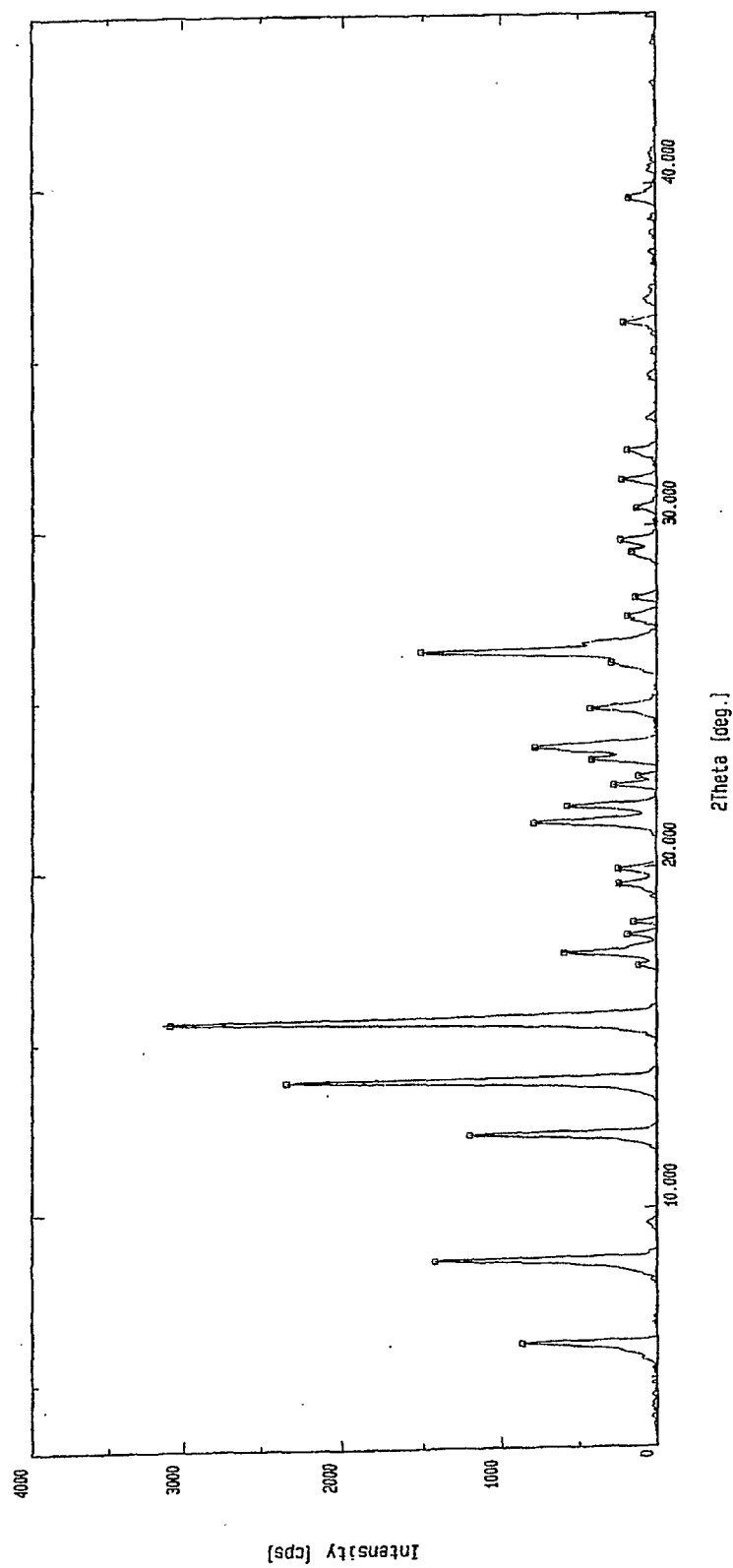


FIG. 8: Fourier Transform Infra Red (FTIR) spectrum for Form II of Compound I

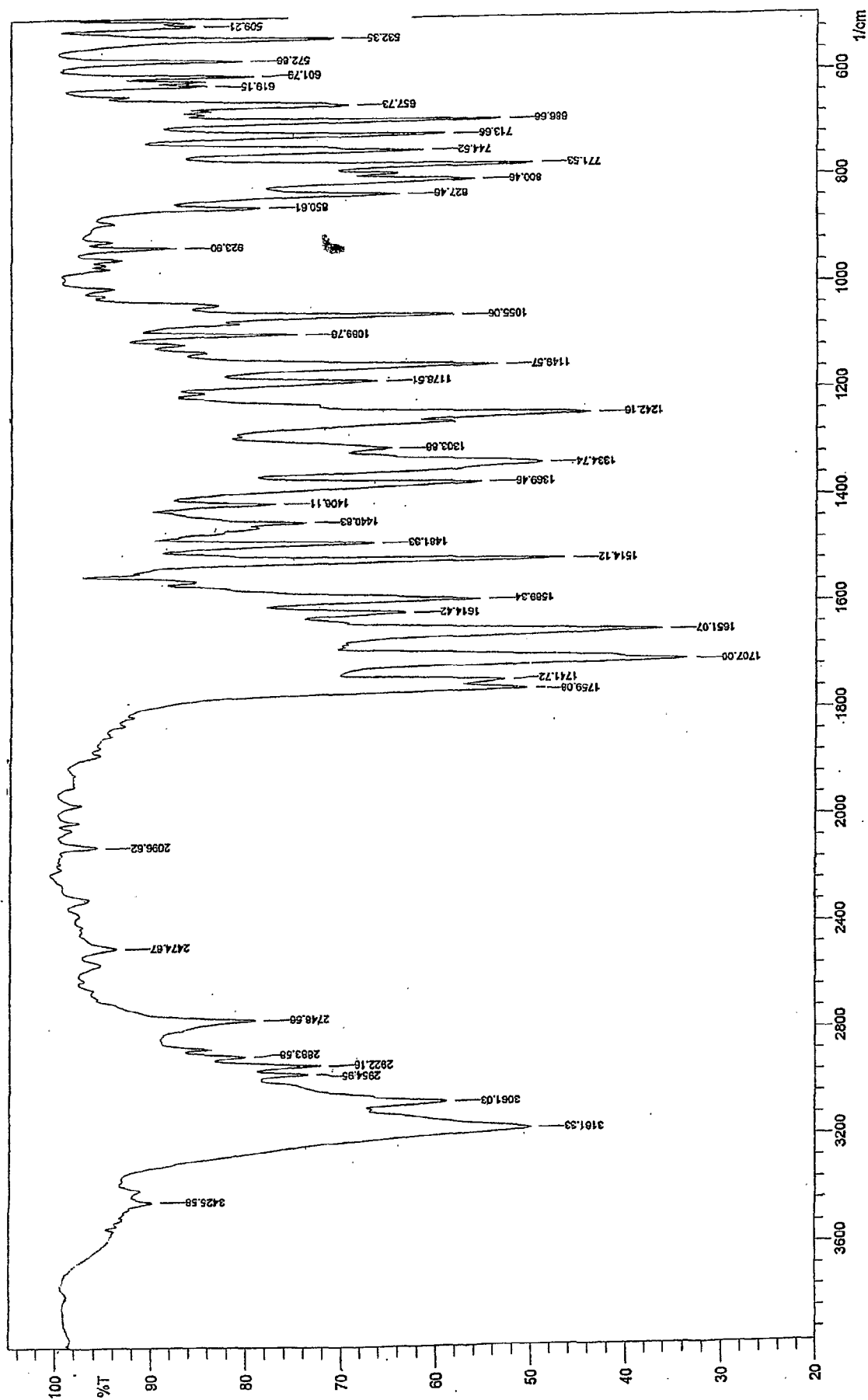


FIG. 9: X-ray powder diffraction pattern (XRPD) for Form 0 of Compound I

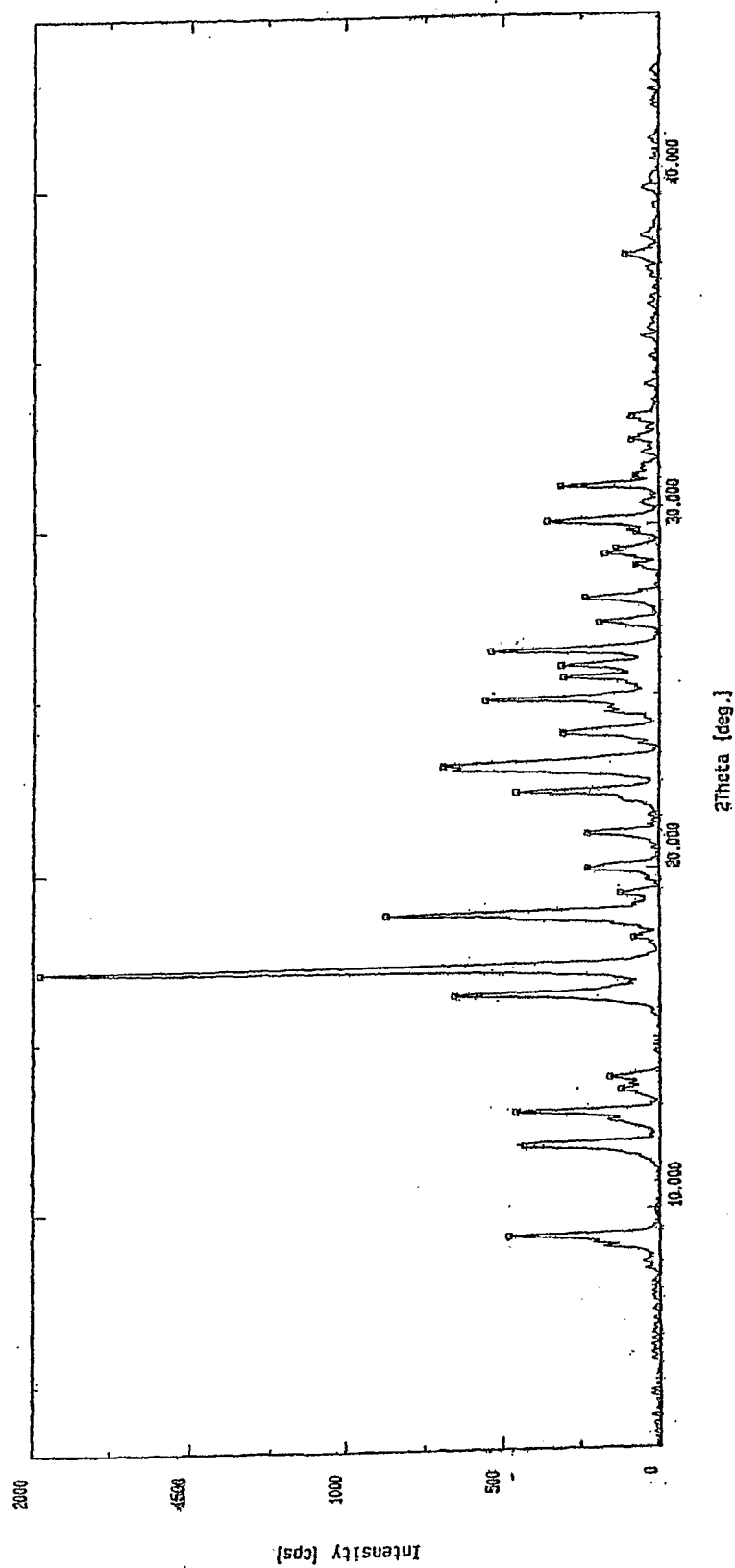


FIG. 10: Fourier Transform Infra Red (FTIR) spectrum for Form 0 of Compound I

