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(71) Applicant: **RESPIVERT LIMITED** [GB/GB]; 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire HP12 4EG (GB).

(72) Inventors: **BROECKX, Rudy, Laurent, Maria**; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse (BE). **FILLIERS, Walter, Ferdinand, Maria**; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse (BE). **NIESTE, Patrick, Hubert, J.**; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse (BE). **COPMANS, Alex, Herman**; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse (BE). **VANHOUTTE, Filip, Marcel, C.**; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse (BE). **LEYS, Carina**; c/o Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse (BE).

(74) Agents: **TEUTEN, Andrew** et al.; Sagittarius IP, Three Globeside, Fieldhouse Lane, Marlow, Buckinghamshire SL7 1HZ (GB).

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(54) **Title**: NOVEL PHARMACEUTICAL FORMULATIONS

(57) **Abstract**: There is provided inter alia a dry powder pharmaceutical formulation for inhalation comprising: (i) 6-(2-((4-amino-3-(3-hydroxyphenyl)-1 H-pyrazolo[3,4-d]pyrimidin-1-yl) methyl)-3- (2-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-N, N-bis(2-methoxyethyl)hex-5- ynamide or a pharmaceutically acceptable salt thereof, including all stereoisomers, tautomers and isotopic derivatives thereof and solvates thereof in particulate form as active ingredient; (ii) particulate lactose as carrier; and (iii) a particulate stabilizing agent selected from metal salts of stearic acid such as magnesium stearate and metal salts of stearyl fumarate.

NOVEL PHARMACEUTICAL FORMULATIONS

Field of the invention

The present invention provides novel dry powder pharmaceutical formulations for inhalation of a compound that inhibits phosphoinositide 3-kinases (PI3 kinases), and their use in therapy, especially in the treatment of inflammatory diseases such as COPD and asthma.

Background of the invention

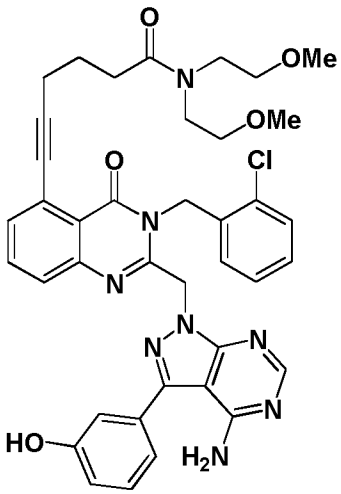
Lipid kinases catalyse the phosphorylation of lipids to produce species involved in the regulation of a wide range of physiological processes, including cellular migration and adhesion. The PI3-kinases are membrane associated proteins and belong to the class of enzymes which catalyse the phosphorylation of lipids which are themselves associated with cell membranes. The PI3-kinase delta isozyme (PI3 kinase δ) is one of four isoforms of type I PI3 kinases responsible for generating various 3′-phosphorylated phosphoinositides, that mediate cellular signalling and has been implicated in inflammation, growth factor signalling, malignant transformation and immunity [See Review by Rameh, L. E. and Cantley, L. C. *J. Biol. Chem.*, **1999**, *274*:8347-8350].

The involvement of PI3 kinases in controlling inflammation has been confirmed in several models using pan-PI3 kinase inhibitors, such as **LY-294002** and wortmannin [Ito, K. *et al.*, *J Pharmacol. Exp. Ther.*, **2007**, 321:1-8]. Recent studies have been conducted using either selective PI3 kinase inhibitors or in knock-out mice lacking a specific enzyme isoform. These studies have demonstrated the role of pathways controlled by PI3 kinase enzymes in inflammation. The PI3 kinase δ selective inhibitor **IC-87114** was found to inhibit airways hyper-responsiveness, IgE release, pro-inflammatory cytokine expression, inflammatory cell accumulation into the lung and vascular permeability in ovalbumin-sensitized, ovalbumin-challenged mice [Lee, K. S. *et al.*, *J. Allergy Clin. Immunol.*, **2006**, 118:403-409 and Lee, K. S. *et al.*, *FASEB J.*, **2006**, 20:455-65]. In addition, **IC-87114** lowered neutrophil accumulation in the lungs of mice and neutrophil function, stimulated by TNFα [Sadhu, C. *et al., Biochem. Biophys. Res. Commun.*, **2003**, 308:764-9]. The PI3 kinase δ isoform is activated by insulin and other growth factors, as well as by G-protein coupled protein signalling and inflammatory cytokines. Recently the PI3 kinase dual δ/γ inhibitor **TG100-115** was reported to inhibit pulmonary eosinophilia and interleukin-13 as well as mucin accumulation and airways hyperesponsiveness in a murine model, when administered by aerosolisation. The same authors also reported that the compound was able to inhibit pulmonary neutrophilia elicited by either LPS or cigarette smoke [Doukas, J. *et al.*, *J Pharmacol. Exp. Ther.,* **2009**, 328:758-765]

Since it is also activated by oxidative stress, the PI3 kinase δ isoform is likely to be relevant as a target for therapeutic intervention in those diseases where a high level of oxidative stress is implicated. Downstream mediators of the PI3 kinase signal transduction pathway include Akt (a serine/threonine protein kinase) and the mammalian target of rapamycin, the enzyme mTOR. Recent work has suggested that activation of PI3 kinase δ, leading to phosphorylation of Akt, is able to induce a state of corticosteroid resistance in otherwise corticosteroid-sensitive cells [To,

Y. *et al., Am. J. Respir. Crit. Care Med.*, **2010**, 182:897-904]. These observations have led to the hypothesis that this signalling cascade could be one mechanism responsible for the corticosteroid-insensitivity of inflammation observed in the lungs of patients suffering from COPD, as well as those asthmatics who smoke, thereby subjecting their lungs to increased oxidative stress. Indeed, theophylline, a compound used in the treatment of both COPD and asthma, has been suggested to reverse steroid insensitivity through mechanisms involving interaction with pathways controlled by PI3 kinase δ [To, Y. *et al., Am. J. Respir. Crit. Care Med.*, **2010**, 182:897-904].

International patent application WO2011/048111 discloses a number of compounds which are inhibitors of PI3 kinases, particularly PI3 kinase δ, including 6-(2-((4-amino-3-(3-hydroxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl) methyl)-3-(2-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-*N*,*N*-bis(2-methoxyethyl)hex-5-ynamide in the free base form which is disclosed therein as Example 83. This compound is also disclosed in WO2012/052753.



(I)

The above mentioned compound is referred to herein as "compound of formula (I)" or "compound of formula (I) free base".

Prior to the applicant's earlier disclosure (WO2011/048111), the PI3 kinase inhibitors described to date have typically been intended for oral administration. However, an undesired consequence of this approach is that non-targeted body tissues, especially the liver and the gut, are likely to be exposed to pharmacologically active concentrations of the drug. An alternative strategy is to design treatment regimens in which the drug is dosed directly to the inflamed organ via topical therapy. In the case of controlling inflammation (or providing another therapeutic effect) in the lungs, this may be achieved by inhalation of the drug, which has the benefit of retaining the drug predominantly in the lungs thereby minimising the risks of systemic toxicity. In order to achieve a sustained duration of action an appropriate formulation which generates a "reservoir" of the active drug may be used.

The compound of formula (I) has, accordingly, been described as being useful for topical administration to the lung (see WO2011/048111).

As well as providing affinity for the target organ and sustained efficacy, a drug for topical administration to the lung via inhalation must also be formulated so as to provide a predictable dose of the drug, which in turn must have predictable and reproducible properties. Achieving acceptable and reproducible chemical and physical stability of the drug in the formulation is a key goal in the product development of pharmaceutical products for all types of pharmaceutical dosage forms.

For inhalation use, there are 3 main dosage forms – a dry powder inhaler (DPI), a metered dose inhaler (MDI) and an aqueous based nebuliser (hand-held or table-top). However the majority of global sales of inhalation products are DPIs and thus provide a well-accepted way of delivering drugs by inhalation. There are numerous commercialised DPI products, such as Flixotide (fluticasone propionate), Advair (fluticasone propionate / salmeterol), Symbicort (budesonide / formoterol), Pulmicort (budesonide), Serevent (salmeterol) and Foradil (formoterol).

Dry powder inhalation formulations typically consist of a blend of drug particles (size below 10 microns and normally below 5 microns) with a diluent, typically lactose. Since the usual doses required for inhaled therapies are in the microgram range, the diluent facilitates pharmaceutical processing and dispensing of individual doses e.g. into capsules or blisters or the metering of doses from a bulk reservoir, for subsequent administration to the patient. Therefore, typically, the mass of diluent (the most common being lactose) may be greater than that of the drug substance. In this environment, acceptable formulations of some products can be achieved by simply blending the drug with lactose. Other products may require other additional excipients or other processing steps in order for the product to meet the requirements of regulatory authorities.

One such additional excipient is magnesium stearate which is known for improving certain properties of formulations containing it. Thus, US7186401B2 (Jagotec AG et al.) discloses that the addition of magnesium stearate to dry powder formulations for inhalation improves the moisture resistance of the formulations and allows a high fine particle dosage or fine particle fraction to be maintained under humid conditions. WO00/53157 (Chiesi) describes magnesium stearate as a lubricant to be employed in dry powder formulations for inhalation which is capable if increasing the fine particle dose of certain drugs. US2006/0239932 (Monteith) discloses an inhalable solid pharmaceutical formulation comprising certain active ingredient substances susceptible to chemical interaction with lactose, lactose and magnesium stearate. It is disclosed that magnesium stearate inhibits lactose induced degradation of the active ingredient, presumably via the Maillard reaction which involves the reaction of an amine group on the active ingredient with lactose. US2012/0082727 (Chiesi) discloses a method of inhibiting or reducing chemical degradation of an active ingredient bearing a group susceptible to hydrolysis selected from the group consisting of a carbonate group, a carbamate group and an ester group in a powder formulation for inhalation comprising carrier particles (such as lactose particles) said method comprising coating at least a portion of the surface of said carrier particles with magnesium stearate.

Thus, there remains a need to provide formulations of selective PI3 kinase inhibitors for use in inhalation therapy which have the potential to provide therapeutic efficacy in asthma, COPD and

other inflammatory diseases of the lungs. In particular, it remains an objective to provide a formulation of the compound of formula (I) which has appropriate physical and chemical stability and other necessary properties for inhalation therapy.

Summary of the invention

In a first aspect, the present invention provides a dry powder pharmaceutical formulation for inhalation comprising:

(i) 6-(2-((4-amino-3-(3-hydroxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl) methyl)-3-(2-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-*N*,*N*-bis(2-methoxyethyl)hex-5-ynamide (compound of formula (I)) or a pharmaceutically acceptable salt thereof, including all stereoisomers, tautomers and isotopic derivatives thereof and solvates thereof in particulate form as active ingredient;

(ii) particulate lactose as carrier; and

(iii) a particulate stabilizing agent selected from metal salts of stearic acid (such as magnesium stearate) and metal salts of stearyl fumarate

Such a formulation is hereinafter referred to as “a formulation of the invention”.

As explained in the Examples, formulations of the invention appear to have good physical stability (as determined by XRPD and IR analysis) and good chemical stability (as determined by HPLC analysis). Without being limited by theory, it appears from the inventors’ discoveries that the alkyne group of the compound of formula (I) is susceptible to metal catalysed oxidative degradation involving hydration of the alkyne. It also appears from the inventors’ discoveries that the pyrimidinone ring of the compound of formula (I) is susceptible to hydrolytic cleavage. Experiments conducted by the inventors have determined that formulations of the invention containing lactose and a metal salt of stearic acid such as magnesium stearate have superior chemical stability than corresponding formulations not containing a metal salt of stearic acid such as magnesium stearate. To the inventors’ knowledge it has not been reported before that a metal salt of stearic acid such as magnesium stearate can act as a protecting agent against chemical degradation of alkyne containing compounds (especially in respect of metal catalysed oxidative degradation involving hydration of the alkyne) in dry powder inhalation formulations. To the inventors’ knowledge it has also not been reported before that a metal salt of stearic acid such as magnesium stearate can act as a protecting agent against hydrolytic cleavage of a drug substance containing a pyrimidinone ring. The inventors extrapolate these findings with metal salts of stearic acid to metal salts of stearyl fumarate.

Brief description of the figures

Figure 1 shows an XRPD pattern acquired on a sample of compound of formula (I) in solid crystalline anhydrous form.

Figure 2 shows an IR spectrum of a sample of a blend of compound of formula (I) in anhydrous form (micronized) with Lactohale200® and magnesium stearate.

Figure 3 shows an XRPD pattern acquired on a sample of a blend of compound of formula (I) in anhydrous form (micronized) with Lactohale200® and magnesium stearate.

Detailed description of the invention

Compound of formula (I) as active ingredient

The compound of formula (I) is a dual PI3K delta PI3K gamma inhibitor, wherein the term inhibitor as employed herein is intended to refer to a compound that reduces (for example by at least 50%) or eliminates the biological activity of the target protein, for example the PI3K delta isozyme, in an *in vitro* enzyme assay. The term delta/gamma inhibitor as employed herein is intended to refer to the fact that the compound inhibits, to some degree, both enzyme isoforms although not necessarily to the same extent. Compound of formula (I) is active in cell based screening systems and thereby demonstrates that it possesses suitable properties for penetrating cells and thereby exert intracellular pharmacological effects.

Generic processes for synthesising the compound of formula (I) are disclosed in WO2011/048111, the contents of which are incorporated by reference in their entirety, and a method similar to that of Example 1 can be employed. See also WO2012/052753, the contents of which are incorporated by reference in their entirety, where a specific method for synthesising the compound of formula (I) is provided in the Example.

Suitably, compound of formula (I) is protected from light during and after synthesis e.g. by use of amber glassware or light impervious packaging (e.g. foil packaging).

The dry powder pharmaceutical formulation of the present invention comprises compound of formula (I) as active ingredient in a therapeutically effective amount. A therapeutically effective amount of compound of formula (I) is defined as an amount sufficient, for a given dose or plurality of divided doses, to achieve a therapeutically meaningful effect in a subject when administered to said subject in a treatment protocol.

In one embodiment, the dry powder pharmaceutical formulation comprises from about 0.004 wt.% to about 50 wt.% of compound of formula (I) based on weight of the dry powder pharmaceutical formulation and based on weight of compound of formula (I) as free base; for example from about 0.02 wt.% to about 50 wt.%, from about 0.02 wt.% to about 25 wt.%, from about 0.02 wt.% to about 20 wt.%, or from about 0.02 wt.% to about 15 wt.%. Preferably, the dry powder pharmaceutical formulation comprises from about 0.1 wt.% to about 20 wt.% e.g. from about 0.1 wt.% to about 5 wt.% of compound of formula (I) based on the weight of the dry powder pharmaceutical formulation and based on weight of compound of formula (I) as free base.

A pharmaceutical formulation of the invention may contain compound of formula (I) as a single active ingredient. However, the pharmaceutical formulation may contain further active ingredients. The pharmaceutical formulation may also be co-administered together with one or more other active ingredients (or one or more pharmaceutical formulations containing one or more active ingredients). Exemplary further active ingredients are mentioned below.

Compound of formula (I) is prepared in particulate form such that it is suitable for dry powder inhalation. A pharmaceutical formulation of the invention may typically contain drug particles having a volume median diameter (D50) from about 0.5 μm to about 10 μm particularly from about 1 μm to about 5 μm.

A suitable method for determining particle size is laser diffraction, e.g. using a Mastersizer 2000S instrument from Malvern Instruments. Instruments are also available from Sympatec. For particle size distributions, the median value D50 is the size in microns that splits the particle size distribution with half above and half below. The primary result obtained from laser diffraction is a volume distribution, therefore D50 is actually Dv50 (median for a volume distribution) and as used herein refers to particle size distributions obtained using laser diffraction. D10 and D90 values (when used in the context of laser diffraction, taken to mean Dv10 and Dv90 values) refer to the particle size wherein 10% of the distribution lies below the D10 value, and 90% of the distribution lies below the D90 value, respectively.

Particles of suitable size for use in a dry powder inhalation formulation may be prepared by any suitable method known to the person skilled in the art. Drug particles of suitable size for inhalation may be prepared by particle size reduction methods including milling or more preferably micronization e.g. using a jet mill micronization device (e.g. as manufactured by Hosokawa Alpine). Alternatively, particulates of suitable size may be produced at the first instance by spray drying, spray freezing, controlled crystallisation approaches e.g. controlled precipitation, super-critical fluid crystallisation, sonocrystallisation or other suitable crystallisation procedure, for example in a continuous crystallisation apparatus.

In one embodiment, compound of formula (I) is in free base form, in the form of a pharmaceutically acceptable salt, or in the form of a solvate of either. Suitably compound of formula (I) is in free base form, e.g. in anhydrous form.

Suitably, compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, is in solid crystalline form.

Pharmaceutically acceptable salts of compound of formula (I)

In one embodiment there is provided a pharmaceutically acceptable salt of compound of formula (I).

The pharmaceutically acceptable salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms that the compound of formula (I) is able to form. These pharmaceutically acceptable acid addition salts conveniently can be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

Thus, specific examples of salts of compound of formula (I) include the acid additional salts formed with HCl, HBr and *p*-toluenesulfonic acid.

Solvates

The invention also extends to solvates of compound of formula (I). Examples of solvates include hydrates and hygroscopic products such as channel hydrates.

Anhydrous form of compound of formula (I)

In one embodiment, there is provided compound of formula (I) in anhydrous form. In particular, there is provided compound of formula (I) in solid crystalline anhydrous form, obtained by crystallizing compound of formula (I) from 1-propanol. Suitably, the 1-propanol is dry e.g. containing a maximum of around 0.9% w/w water. In one embodiment, the 1-propanol has a maximum of 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2% or 0.05% w/w of water. Suitably, the 1-propanol has maximum of 0.2% water. Suitably, crystallisation is performed in the presence of a metal scavenger. Suitable metal scavengers are materials that adsorb the metal while being easily separable from the compound of interest (i.e. compound of formula (I)). For example, functionalised silicas are particularly useful as metal scavengers, as once the metal has been adsorbed, the metal-silica complex may then be easily separated from the compound of interest by filtration. Functional groups that form stable complexes with metal ions include groups containing one or more nitrogen and/or sulphur centres, and are well known to the person skilled in the art.

An example of a suitable commercially available metal scavenger is SiliaMetS® Thiol (a thiol-derivatised silica gel suitable for scavenging a variety of metals including Pd, Pt, Cu, Ag and Pb). Suitably, the metal scavenger is present in an amount sufficient to ensure that the resulting metal ion concentration is below 20 ppm, preferably below 10 ppm. In one embodiment, the metal scavenger is present at 1-10% w/w, for example 2-8% w/w or 5% w/w based on weight of compound of formula (I). Suitably crystallisation is performed by cooling the solution of compound of formula (I) and solvent from elevated temperature (e.g. 80-95°C), continuously (i.e. continuous cooling) or in stages (i.e. alternating between cooling and holding solution at a particular temperature). Suitable temperature gradients (continuous or separate) for cooling include 95-15°C, 95-20°C, 90-20°C, 80-20°C 95-90°C, 95-85°C, 95-80°C 90-85°C and 80-20°C. In one embodiment, the solution is cooled from around 80-95°C to ambient temperature (e.g. around 20-22°C). The detailed preparation of such a solid crystalline anhydrous form of compound of formula (I) is provided in Example 2. Crystals of compound of formula (I) in solid crystalline form may be collected by usual separation techniques (e.g. by filtration or centrifugation).

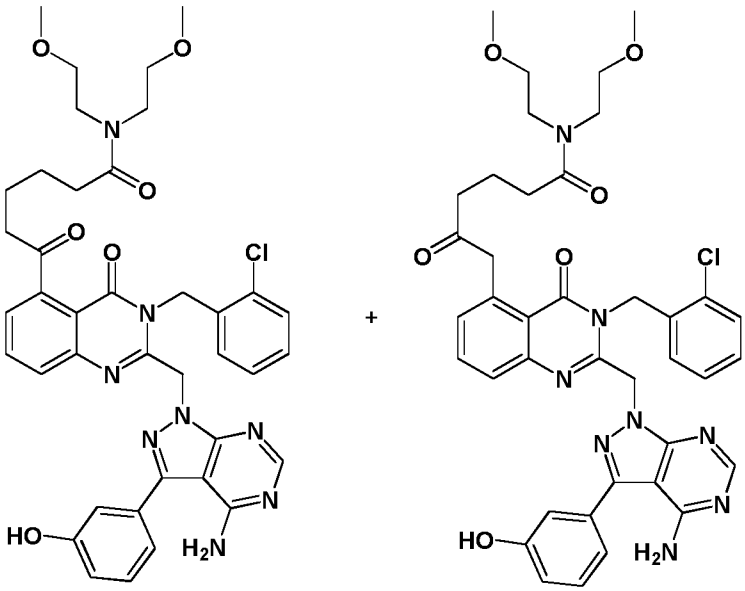
In one embodiment, there is provided a solid crystalline anhydrous form of compound of formula (I) having an XRPD pattern substantially as shown in Figure 1. The method of obtaining the XRPD data is described in the General Procedures and the data discussed in Example 3.

Thus, there is provided compound of formula (I) in a crystalline anhydrous form having an X-ray powder diffraction pattern with at least one (for example, one, two, three, four, five, six, seven, eight, nine or all ten) peaks at 5.6, 7.9, 11.2, 12.3, 15.6, 17.6, 18.4, 21.4, 22.5, 24.2 (± 0.2

degrees, 2-theta values), these peaks being characteristic of the crystalline anhydrous form. The peaks at 17.6, 18.4, 22.5 and 24.2 are particularly characteristic for the anhydrous form and therefore it is preferred to see at least one (for example one, two, three or all four) of these peaks.

The chemical compatibility of the anhydrous form of compound(I) with lactose was investigated.

In order to assess chemical compatibility, compositions of the anhydrous form of compound of formula (I) with lactose were analysed by HPLC. The results are summarised in Example 4 where it is indicated that under certain conditions the composition of anhydrous form and lactose underwent degradation. The degradation products were investigated and the main degradant was identified by mass spectrometry as being one or both of the two substances shown as D019328:



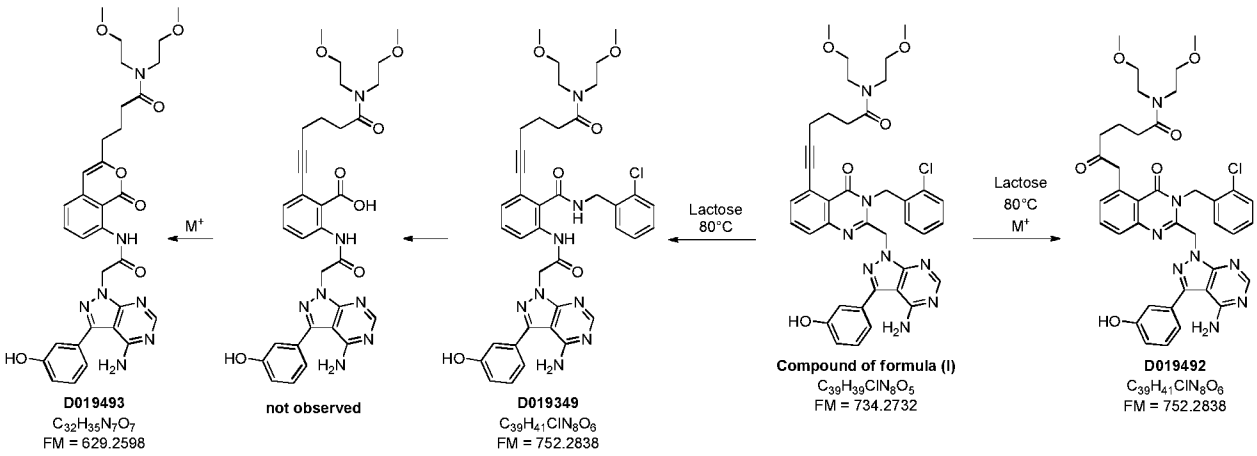
D019328
$C_{39}H_{41}ClN_8O_5$
FM = 752.2838

This degradation product is likely to be the result of the addition of water across the alkyne triple bond and may exist as one of two forms with identical mass (or may exist in both forms), depending on the orientation of the addition of the water across the triple bond. The same degradant has been observed during the forced degradation of the anhydrous form of compound of formula (I) with metal ions. As a result of further studies, it appears that the degradation of the anhydrous form of compound of formula (I) requires metal ions and water and is accelerated by elevated temperature.

Further investigation involving accelerated stability testing (i.e. exposure of the drug substance to 80 °C in a closed vial, see Example 7) has led the inventors to confirm that at least the degradation product shown as D019492 in Scheme 1 (below) is generated. Moreover the inventors also concluded that a further degradation product (D019493) can result from the

hydrolytic cleavage of the pyrimidinone ring and subsequent intramolecular reaction with the alkyne group. D019349 is a presumed intermediary degradation product which was observed in certain circumstances of temperature and RH in stability testing (data not shown).

Scheme 1



The addition of magnesium stearate to the combination of anhydrous form of compound of formula (I) and lactose was investigated. The combination of anhydrous form of compound of formula (I) with lactose and magnesium stearate was found to be physically stable (Example 5). However, surprisingly, it was found that the addition of magnesium stearate caused an increase in the chemical stability of the combination of anhydrous form of compound of formula (I) and lactose (Example 6). A similar stabilising effect was found using other metal salts of stearic acid, specifically sodium stearate and calcium stearate (Example 7).

Without wishing to be bound by theory, it appears that the metal salt of stearic acid such as magnesium stearate (or, it is believed, a metal salt of stearyl fumarate) can act as a protecting agent against chemical degradation of the alkyne group in the compound of formula (I) and against chemical degradation of the pyrimidinone ring in the compound of formula (I) which is observed when the anhydrous form of compound of formula (I) is in a mixture with lactose.

Particulate lactose as carrier

As used herein, the term "lactose" refers to a lactose-containing component, including α-lactose monohydrate, β-lactose monohydrate, α-lactose anhydrous, β-lactose anhydrous and amorphous lactose. Lactose components may be processed by micronization, sieving, milling, compression, agglomeration or spray drying. Commercially available forms of lactose in various forms are also encompassed, for example Lactohale® (inhalation grade lactose; Frieslandfoods), InhaLac®70 (sieved lactose for dry powder inhaler; Meggle) and Respitose® (sieved inhalation grade lactose; DFE Pharma) products. In one embodiment, the lactose component is selected from the group consisting of α-lactose monohydrate, α-lactose anhydrous and amorphous lactose. Preferably, the lactose is α-lactose monohydrate.

In order to penetrate sufficiently far into the lungs, the particulate active ingredient (in this case compound (I)) must be a suitable size as described above. These small particles will have a

tendency to agglomerate. The use of a carrier such as lactose prevents this agglomeration and can improve flowability. Furthermore, the use of a carrier ensures that a correct and consistent dosage reaches the lungs. The active ingredient will usually form a monolayer on the larger lactose particle, then during inhalation the active ingredient and the carrier are separated and the active ingredient is inhaled, while the majority of the carrier is not. As such, the use of particulate lactose as a carrier for the active ingredient ensures that each dose of the dry powder pharmaceutical formulation releases the same amount of the active ingredient.

Generally, to prevent agglomeration of the small active particles, lactose with a particle size of approximately or at least ten times that of the active ingredient is used (e.g. lactose having a D50 approximately or at least ten times that of the active ingredient is used).

In one embodiment, the dry powder formulation of the present invention comprises particulate lactose having D50 in the range 40-150 µm.

The dry powder pharmaceutical formulation of the present invention comprises particulate lactose as carrier in an amount sufficient to ensure that the correct and consistent dosage of the active ingredient reaches the lungs. In one embodiment, the dry powder pharmaceutical formulation comprises from about 40 wt.% to about 99.88 wt.%, for example from about 50 wt.% to about 99.88 wt.%, for example from about 65 wt.% to about 99.88 wt.%, for example from about 75 wt.% to about 99.99 wt.% of particulate lactose based on the weight of the dry powder pharmaceutical formulation. Preferably, the dry powder pharmaceutical formulation comprises from about 80 wt.% to about 99.98 wt.% or for example from about 80 wt % to about 99.9% wt %, for example from about 85 wt.% to about 99.98 wt.%, for example from about 95 wt.% to about 99 wt.% of particulate lactose based on the weight of the dry powder pharmaceutical composition.

Particulate metal salt of stearic acid such as magnesium stearate or metal salt of stearyl fumarate as stabilizing agent

An example metal salt of stearic acid is magnesium stearate.

Alternative metal salts of stearic acid that may be employed include salts of stearic acid formed with Group I and other Group II metals, such as sodium stearate, calcium stearate and lithium stearate. Other metal salts of stearic acid that may be mentioned include zinc stearate and aluminium stearate.

Metal salts of stearyl fumarate (e.g. sodium stearyl fumarate) appear to have similar properties to those of metal salts of stearic acid (see Shah et al, Drug development and Industrial pharmacy 1986, Vol. 12 No. 8-9 , 1329-1346). In the inventors' opinion they can be employed as an alternative to metal salts of stearic acid in the present invention.

As used herein the term "magnesium stearate" includes magnesium stearate trihydrate, magnesium stearate dihydrate, magnesium stearate monohydrate and amorphous magnesium stearate. Magnesium stearate as defined herein includes a tolerance wherein any material

defined as "magnesium stearate" may contain up to 25% (e.g. up to 10% e.g. up to 5% e.g. up to 1%) of palmitate salt.

More generally, metal salts of stearic acid or metal salts of stearyl fumarate may be employed in anhydrous form or as a hydrate and may contain up to 25% (e.g. up to 10% e.g. up to 5% e.g. up to 1%) of palmitate salt.

As used herein the expression "stabilizing agent selected from metal salts of stearic acid such as magnesium stearate and metal salts of stearyl fumarate" can include a mixture of metal salts of stearic acid and/or stearyl fumarate, although use of a single salt would be preferred.

The metal salt of stearic acid such as magnesium stearate or metal salt of stearyl fumarate is typically obtained as a fine powder which need not be micronized. Suitably the D50 of the metal salt of stearic acid such as magnesium stearate or the metal salt of stearyl fumarate is greater than 5 μm e.g. around 10 μm or greater than 10 μm e.g. in the range 5 to 100 μm e.g. 5 to 50 μm e.g. 5 to 20 μm e.g. 10 to 20 μm. Magnesium stearate may for example be obtained from Avantor (Hyqual 2257 brand) or Peter Greven. Sodium stearate and calcium stearate may, for example, be obtained from Sigma-Aldrich. Sodium stearyl fumarate may, for example, be obtained from ScienceLab.

The dry powder pharmaceutical formulation of the present invention comprises particulate stabilizing agent selected from metal salt of stearic acid such as magnesium stearate and metal salts of stearyl fumarate in an amount sufficient to ensure the chemical stability of the formulation ("a stabilising amount"). Chemical stability is, for example, demonstrated when the production of degradant D019328 (one or both substances) is at a level of less than 0.2% wt. % following storage of the composition containing Compound of formula (I) for 4 weeks at 50 ^{o}C. Alternatively or in addition, chemical stability is, for example, demonstrated when the production of degradant D019493 is at a level of less than 0.5% wt. % following storage of the composition containing compound of formula (I) for 2 weeks at 80 ^{o}C. Alternatively, or in addition, chemical stability is, for example, demonstrated when the production of degradant D019492 is at a level of less than 0.4% wt. % following storage of the composition containing Compound of formula (I) for 2 weeks at 80 ^{o}C. In one embodiment, the dry powder pharmaceutical formulation comprises from about 0.01 wt.% to about 15 wt.%, for example 0.1 wt.% to about 10 wt.%, 10 wt.%, 5 wt.%, 2 wt.% or 1 wt.% of particulate stabilizing agent selected from metal salt of stearic acid such as magnesium stearate and metal salts of stearyl fumarate based on the weight of the dry powder pharmaceutical formulation. Preferably, the dry powder pharmaceutical formulation comprises from about 0.5 wt.% to about 5 wt.% e.g. 1-2% w/w of particulate stabilizing agent selected from metal salt of stearic acid such as magnesium stearate and metal salts of stearyl fumarate based on the weight of the dry powder pharmaceutical composition. Suitably, the stabilizing agent selected from metal salt of stearic acid such as magnesium stearate and metal salts of stearyl fumarate is present in an amount sufficient to ensure the physical stability of the formulation. Physical stability is, for example, demonstrated when the IR spectrum and XRPD pattern of the composition (especially in relation to characteristics peaks of Compound of formula (I)) are substantially unaltered following storage of the composition containing Compound of formula (I) for 4 weeks at 50 ^{o}C.

In one embodiment, the dry powder pharmaceutical formulation for inhalation of the present invention comprises:

(i) from about 0.02 to 50 wt.% 6-(2-((4-amino-3-(3-hydroxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl) methyl)-3-(2-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-*N*,*N*-bis(2-methoxyethyl)hex-5-ynamide or a pharmaceutically acceptable salt thereof, including all stereoisomers, tautomers and isotopic derivatives thereof and solvates thereof in particulate form as active ingredient;

(ii) from about 40 wt.% to about 99.88 wt.% particulate lactose; and

(iii) from about 0.1 wt.% to about 10 wt.% particulate stabilizing agent selected from metal salts of stearic acid (such as magnesium stearate) and metal salts of stearyl fumarate.

In a further embodiment, the dry powder pharmaceutical formulation for inhalation of the present invention comprises:

(i) from about 0.02 to 50 wt.% 6-(2-((4-amino-3-(3-hydroxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl) methyl)-3-(2-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-*N*,*N*-bis(2-methoxyethyl)hex-5-ynamide in free base form;

(ii) from about 40 wt.% to about 99.88 wt.% particulate lactose; and

(iii)from about 0.1 wt.% to about 10 wt.% particulate stabilizing agent selected from metal salts of stearic acid (such as magnesium stearate) and metal salts of stearyl fumarate.

A further aspect of the invention relates to the use of a stabilizing agent selected from metal salt of stearic acid such as magnesium stearate and metal salts of stearyl fumarate in a pharmaceutical formulation containing a compound of formula (I) and lactose to increase the stability of the compound of formula (I) to chemical degradation (particularly in respect of metal ion catalysed addition of water to the alkyne group and/or hydrolysis of the pyrimidinone ring of the compound of formula (I)) and to a method of increasing the stability of a pharmaceutical formulation containing a compound of formula (I) and lactose to chemical degradation (particularly in respect of metal ion catalysed addition of water to the alkyne group and/or hydrolysis of the pyrimidinone ring of the compound of formula (I)) which comprises including in said formulation a stabilizing amount of a stabilizing agent selected from metal salts of stearic acid such as magnesium stearate and metal salts of stearyl fumarate. Suitably the compound of formula (I) is in solid crystalline anhydrous form.

The preferred stabilizing agent is magnesium stearate.

Pharmaceutical uses and methods of administration

There is provided according to one aspect of the present invention use of pharmaceutical formulation of the invention as a PI3 kinase inhibitor.

In one embodiment there is provided the use of a pharmaceutical formulation of the invention for the treatment of COPD and/or asthma, in particular COPD or severe asthma, by inhalation i.e. by topical administration to the lung. Advantageously, administration to the lung allows the

beneficial effects of the compounds to be realised whilst minimising the side-effects, for patients.

In one embodiment the pharmaceutical formulation of the invention is suitable for sensitizing patients to treatment with a corticosteroid.

The pharmaceutical formulations may conveniently be administered in unit dosage form and may be prepared by any of the methods well-known in the pharmaceutical art, for example as described in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA., (1985).

Topical administration to the lung is achieved by use of an inhalation device.

Thus, an aspect of the invention includes an inhalation device comprising one or more doses of a pharmaceutical formulation according to the invention. Inhalation devices for dry powder formulations are typically breath operated such that the dose is withdrawn from the device and administered to the subject using the power of the subject's lungs by inhaling from a mouthpiece. However, optionally, external energy may be provided to assist the administration of the dose. Typically the inhalation device will comprise a plurality of doses of a pharmaceutical formulation according to the invention, e.g. 2 or 4 or 8 or 28 or 30 or 60 or more doses. Thus the inhalation device may comprise a month's supply of doses. Optionally the doses are divided e.g. such that a dose is administered using two (or more) inhalations from the inhalation device. According to one embodiment of the invention the doses of formulation are pre-metered in the inhalation device. For example the pre-metered doses may be contained in the pouches of a blister strip or disk or within capsules. In an embodiment, a dose is metered into a capsule for use one by one in an inhalation device adapted to deliver the contents of a capsule to a subject upon inhalation. According to another embodiment of the invention the doses are metered in use. Thus the inhalation device contains a reservoir of dry powder and the device meters a dose of powder (typically on a fixed volume basis) prior to or at the time of administration.

Example dry powder inhalation devices include SPINHALER, ECLIPSE, ROTAHALER, HANDIHALER, AEROLISER, CYCLOHALER, BREEZHALER/NEOHALER, FLOWCAPS, TWINCAPS, X-CAPS, TURBOSPIN, ELPENHALER, DISKHALER, TURBUHALER, MIATHALER, TWISTHALER, NOVOLIZER, DISKUS, SKYEHALER, ORIEL dry powder inhaler, MICRODOSE, ACCUHALER, PULVINAL, EASYHALER, ULTRAHALER, TAIFUN, PULMOJET, OMNIHALER, GYROHALER, TAPER, CONIX, XCELOVAIR, PROHALER and CLICKHALER. Another example is MONODOSE inhaler.

Optionally the inhalation device may be over-wrapped for storage to protect against ingress of moisture. A desiccant may optionally be employed within an over-wrap or within the device. Suitably the pharmaceutical formulation according to the invention in the inhalation device is protected from light.

The pharmaceutical formulations according to the invention may also be useful in the treatment of respiratory disorders including COPD, chronic bronchitis, emphysema), asthma, paediatric asthma, cystic fibrosis, sarcoidosis and idiopathic pulmonary fibrosis and especially asthma, chronic bronchitis and COPD.

The pharmaceutical formulations according to the invention may comprise compound of formula (I) as the sole active ingredient, or may comprise additional active ingredients, e.g. active ingredients suitable for treating the above mentioned conditions. For example possible combinations for treatment of respiratory disorders include combinations with steroids (e.g. budesonide, beclomethasone dipropionate, fluticasone propionate, mometasone furoate, fluticasone furoate, flunisolide, ciclesonide, triamcinolone), beta agonists (e.g. terbutaline, bambuterol, salbutamol, levalbuterol, salmeterol, formoterol, clenbuterol, fenoterol, broxaterol, indacaterol, reproterol, procaterol, vilanterol) and/or xanthines (e.g. theophylline), muscarinic antagonists, (e.g. ipratropium, tiotropium, oxitropium, glycopyrronium, glycopyrrolate, aclidinium, trospium), leukotriene antagonists (e.g. zafirlukast, pranlukast, zileuton, montelukast) and/or a p38 MAP kinase inhibitor. It will be understood that any of the aforementioned active ingredients may be employed in the form of a pharmaceutically acceptable salt.

In one embodiment, the pharmaceutical formulation of the invention is administered in combination with an antiviral agent, for example acyclovir, oseltamivir (Tamiflu®), zanamivir (Relenza®) or interferon.

In one embodiment the combination of compound of formula (I) and other active ingredient(s) are co-formulated in the pharmaceutical formulation of the invention. In another embodiment, the other active ingredient(s) are administered in one or more separate pharmaceutical formulations.

In one embodiment compound of formula (I) is co-formulated in the pharmaceutical formulation of the invention or co-administered in a separate formulation with a corticosteroid, for example for use in maintenance therapy of asthma, COPD or lung cancer including prevention of the latter.

In one embodiment the pharmaceutical formulation of the invention is administered by inhalation and a corticosteroid is administered orally or by inhalation either in combination or separately.

The pharmaceutical formulation of the invention may also re-sensitise the patient's condition to treatment with a corticosteroid, when previously the patient's condition had become refractory to the same.

In one embodiment of the invention a dose of the pharmaceutical formulation employed is equal to that suitable for use as a monotherapy but administered in combination with a corticosteroid.

In one embodiment a dose of the pharmaceutical formulation which would be sub-therapeutic as a single agent is employed, and is administered in combination with a corticosteroid, thereby

restoring patient responsiveness to the latter, in instances where the patient had previously become refractory to the same.

Additionally, the pharmaceutical formulation of the invention may exhibit anti-viral activity and prove useful in the treatment of viral exacerbations of inflammatory conditions such as asthma and/or COPD.

The pharmaceutical formulation of the present invention may also be useful in the prophylaxis, treatment or amelioration of influenza virus, rhinovirus and/or respiratory syncytial virus.

In one embodiment the presently disclosed pharmaceutical formulations are useful in the treatment or prevention of cancer, in particular lung cancer, especially by topical administration to the lung.

Thus, in a further aspect, the present invention provides a pharmaceutical formulation as described herein for use in the treatment of one or more of the above mentioned conditions.

In a further aspect, the present invention provides a pharmaceutical formulation as described herein for the manufacture of a medicament for the treatment of one or more of the above mentioned conditions.

In a further aspect, the present invention provides a method of treatment of the above mentioned conditions which comprises administering to a subject an effective amount of a pharmaceutical formulation of the invention thereof.

Pharmaceutical formulations described herein may also be used in the manufacture of a medicament for the treatment of one or more of the above-identified diseases.

The word “treatment” is intended to embrace prophylaxis as well as therapeutic treatment.

Unless otherwise specified, % values as used herein are % values by weight (wt.%).

Pharmaceutical formulations of the invention may have the advantage that they have improved physical stability (e.g. as measured by XRPD and/or IR analysis), improved chemical stability (e.g. as measured by HPLC), improved physical compatibility with lactose, improved chemical compatibility with lactose, improved particle size distribution on administration (such as evidenced by improved fine particle mass) or may have other favourable properties as compared with similar formulations that do not contain a stabilizing agent selected from metal salt of stearic acid such as magnesium stearate and metal salts of stearyl fumarate.

Abbreviations

aq	aqueous
COPD	chronic obstructive pulmonary disease
d	doublet

DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
DPI	dry powder inhaler
DSC	differential scanning calorimetry
DVS	dynamic vapour sorption
EDC.HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
(ES^+)	electrospray ionization, positive mode
EtOAc	ethyl acetate
HPLC	high performance liquid chromatography
HPLC-MS	high performance liquid chromatography mass spectrometry
hr	hour(s)
IR	infrared
LPS	lipopolysaccharide
$(M+H)^+$	protonated molecular ion
MDI	metered dose inhaler
MeOH	methanol
MEK	methylethylketone
MHz	megahertz
min	minute(s)
mm	Millimetre(s)
ms	mass spectrometry
mTOR	mammalian target of rapamycin
m/z	mass-to-charge ratio
NH_4OAc	ammonium acetate
NMR	nuclear magnetic resonance (spectroscopy)
$Pd(dppf)Cl_2$	1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
ppm	parts per million
q	quartet
quin	quintet
RH	relative humidity
RRT	relative retention time
R^t	retention time
RT	room temperature
s	singlet
t	triplet
TBDMSCl	*tert*-butyldimethylsilyl chloride
TGA	thermogravimetric analysis
TNFα	tumour necrosis factor alpha
XRPD	X-ray powder diffraction

EXAMPLES

General Procedures

HPLC-MS

Performed on Agilent HP1200 systems using Agilent Extend C18 columns, (1.8 µm, 4.6 x 30 mm) at 40°C and a flow rate of 2.5-4.5 mL min^{-1}, eluting with a H_2O-MeCN gradient containing 0.1% v/v formic acid over 4 min. Gradient information: 0-3.00 min, ramped from 95% H_2O-5% MeCN to 5% H_2O-95% MeCN; 3.00-3.01 min, held at 5% H_2O-95% MeCN, flow rate increased to 4.5 mL min^{-1}; 3.01–3.50 min, held at 5% H_2O-95% MeCN; 3.50–3.60 min, returned to 95% H_2O-5% MeCN; flow rate reduced to 3.50 mL min^{-1}; 3.60-3.90 min, held at 95% H_2O-5% MeCN; 3.90-4.00 min, held at 95% H_2O-5% MeCN, flow rate reduced to 2.5 mL min^{-1}. UV detection was performed at 254 nm using an Agilent G1314B variable wavelength detector.

Mass spectra (MS)

Obtained using electrospray ionization (ESI) over the range m/z 60 to 2000 at a sampling rate of 1.6 sec/cycle using an Agilent G1956B, over m/z 150 to 850 at a sampling rate of 2 Hz using a Waters ZMD or over m/z 100 to 1000 at a sampling rate of 2 Hz using a Shimadzu 2010 LC-MS system.

NMR spectra

^1H NMR spectra (except those of Example 7) were acquired on a Bruker Avance III spectrometer at 400 MHz using residual undeuterated solvent as reference.

The ^1H NMR spectrum for Example 7 was acquired on a Bruker Avance spectrometer at 600 MHz using residual undeuterated solvent as reference.

X-Ray Powder Diffraction (XRPD)

XRPD patterns were acquired on a PANalytical (Philips) X'PertPRO MPD diffractometer equipped with a Cu LFF X-ray tube (45 kV; 40 mA; Bragg-Brentano; spinner stage) were acquired using Cu Kα radiation and the following measurement conditions:

scan mode:	continuous
scan range:	3 to 50º 2θ
step size:	0.02º/step
counting time:	30 sec/step
spinner revolution time:	1 sec
radiation type:	CuKα
Incident beam path	
program. divergence slit:	15 mm
Soller slit:	0.04 rad
beam mask:	15 mm
anti scatter slit:	1º
beam knife:	+
Diffracted beam path	
long anti scatter shield:	+
Soller slit:	0.04 rad
Ni filter:	+
detector:	X'Celerator

Samples were prepared by spreading on a zero background sample holder.

Infrared spectrometry (IR)

Micro Attenuated Total Reflectance (microATR) was used and the sample was analyzed using a suitable microATR accessory and the following measurement conditions:

apparatus: Thermo Nexus 670 FTIR spectrometer
number of scans: 32
resolution: 1 cm^{-1}
wavelength range: 4000 to 400 cm^{-1}
detector: DTGS with KBr windows
beamsplitter: Ge on KBr
micro ATR accessory: Harrick Split Pea with Si crystal

Chemical stability – High Performance Liquid Chromatography (HPLC)

HPLC analysis was carried out using the following operating conditions:

Column: Waters Xbridge C18 (150 x 3.0 x 3.5 mm) or equivalent (a column is considered equivalent if performance as specified in SST is met and a comparable separation of all relevant compounds is demonstrated).
Column temperature: 35°C
Sample temperature: 10°C
Flow rate: 0.45 ml/min
Injection volume: The injection volume can be adjusted as long as the qualification limits of the system are not exceeded (detector and injector) and the peak shape of the main compound is acceptable. As a guide, 30 µl is considered suitable.
Detection: UV detection at 255 nm
Mobile phase: Preparation and composition:
A: 10 mM ammonium acetate (0.771 g/l) + 0.1%, v/v trifluoroacetic acid in water
B: Acetonitrile
Gradient: Analytical run time is 41 minutes

Solvent	Time (minutes)					
	0	35	36	41	42	48
%A	95	30	0	0	95	95
%B	5	70	100	100	5	5

With this HPLC method the degradant D019492 elutes at RRT0.86.

Chemical stability – Ultra High Pressure Liquid Chromatography (UPLC)

UPLC analysis was carried out using the following operating conditions:

Column: Acquity BEH C_{18}; 2.1 x 150 mm; 1.7 µm or equivalent (a column is considered equivalent if performance as specified in SST is met and a comparable separation of all relevant compounds is demonstrated)
Column temperature: 35°C
Sample temperature: 10°C

Flow rate 0.40 ml/min

Injection volume The injection volume can be adjusted as long as the qualification limits of the system are not exceeded (detector and injector) and the peak shape of the main compound is acceptable. As a guide, 4 µl is considered suitable.

Detection UV detection at 255 nm

Mobile phase Preparation and composition:

A 10 mM ammonium acetate (0.771 g/l) + 0.1%, v/v trifluoroacetic acid in water

B Acetonitrile

Gradient Analytical run time is 23 minutes

Solvent	Time (minutes)					
	0	19	20	23	23.5	28
%A	95	30	0	0	95	95
%B	5	70	100	100	5	5

With this UPLC method the degradant D019492 elutes at RRT = 0.92 -0.93 and the degradant D019493 elutes at RRT = 0.86-0.87.

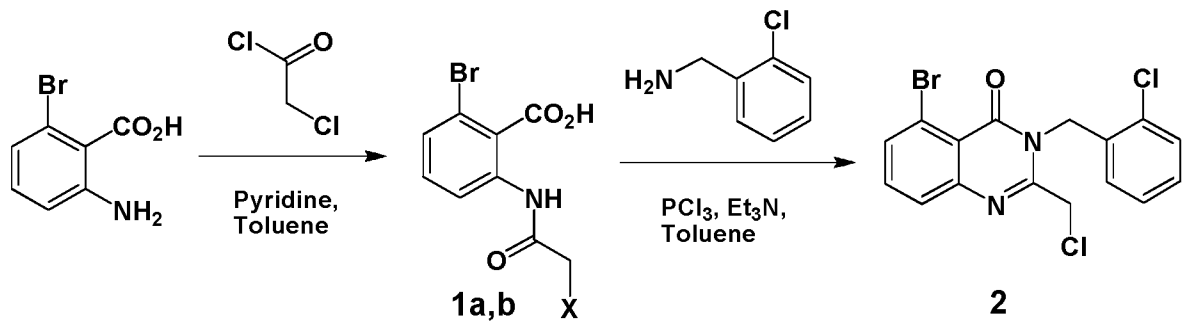
Reagents and suppliers

Lactohale200®: supplied by Frieslandfoods. Particle size (Sympatec): D10: 5-15 µm; D50: 50-100 µm; D90: 120-160 µm.

Magnesium stearate: Grade Hyqual® 2257; supplied by Avantor. Particle size: D10: typically 3 µm; D50: typically 11.5 µm (10.5 – 16.5 µm); D90: typically 24 µm (18 – 28 µm). Supplied as a fine powder.

Example 1 – Preparation of 6-(2-((4-amino-3-(3-hydroxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl) methyl)-3-(2-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-*N*,*N*-bis(2-methoxyethyl)hex-5-ynamide

*5-Bromo-3-(2-chlorobenzyl)-2-(chloromethyl)quinazolin-4(3H)-one (**2**).*

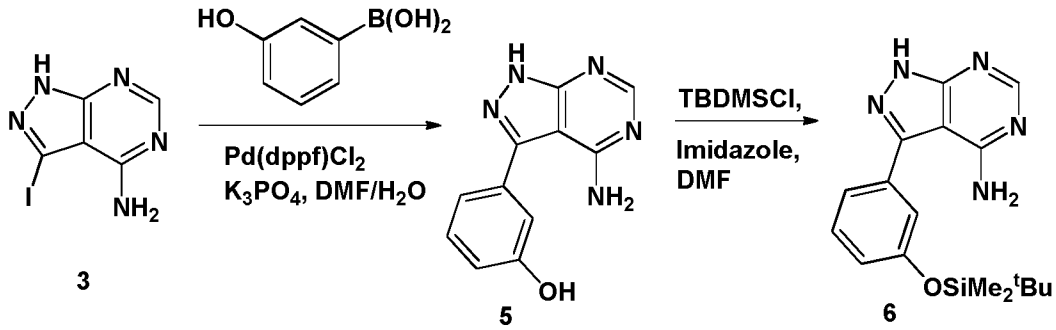


To a stirred solution of 2-amino-6-bromo-benzoic acid (3.06 g, 14.2 mmol) in toluene (75 mL) cooled to 0°C in an ice-bath was added pyridine (0.60 mL, 7.10 mmol) followed by a solution of chloroacetyl chloride (2.26 mL, 28.4 mmol) in toluene (75 mL) drop-wise over 1 hr. The reaction mixture was allowed to warm to RT, and was heated at 115°C for 3 hr and then allowed to cool to RT. The solvent volume was reduced by half by evaporation *in vacuo*. Upon standing overnight, the product precipitated and was collected by filtration to afford 2-bromo-6-(2-

chloroacetamido)benzoic acid (**1a, X = Cl**) (1.44 g) as a white solid: m/z 290/292 $(M+H)^+$ (ES^+). The filtrate was concentrated *in vacuo* and the residue triturated with ethanol/heptane to afford 2-bromo-6-(2-hydroxyacetamido) benzoic acid (**1b X =OH**) (1.02 g, combined yield, 59%): m/z 274/276 $(M+H)^+$ (ES^+). Both **1a** and **1b** can be used without further purification in the next step.

To a stirred mixture of compound (**1a**) (7.50 g, 27.4 mmol), 2-chlorobenzylamine (5.00 mL, 41.05 mmol) and triethylamine (5.70 mL, 41.1 mmol) in toluene (250 mL) was added a solution of phosphorus trichloride (2.60 mL, 30.1 mmol) in toluene (250 mL) dropwise over 1 hr. The reaction mixture was heated to 110°C for 24 hr, whereupon the hot solution was decanted and concentrated *in vacuo*. The residue was triturated with propan-2-ol (50 mL) to afford the title compound (**2**) (6.41 g, 59%) as a yellow solid: R^t 2.67 min; m/z 397/399 $(M+H)^+$ (ES^+).

*3-(3-(tert-Butyldimethylsilyloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**6**).*

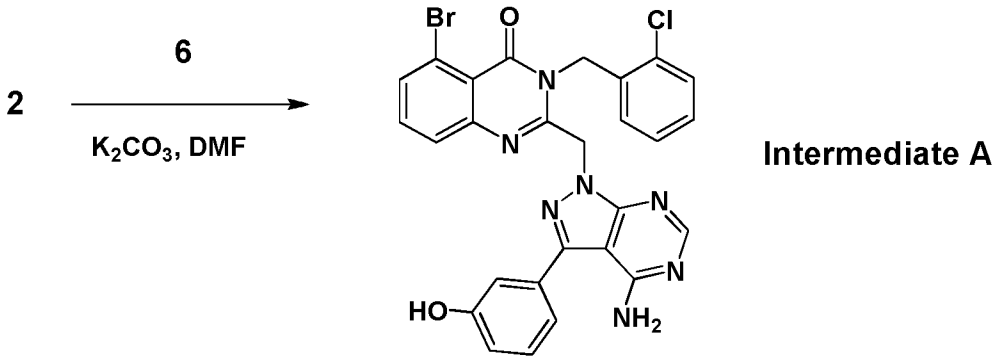


3 **5** **6**

To a stirred suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (**3**) (8.22 g, 31.5 mmol), 3-phenol boronic acid (13.0 g, 94.5 mmol) and potassium phosphate (10.0 g, 47.3 mmol) in degassed DMF/water (3:2, 140 mL) was added $Pd(dppf)Cl_2$ (13.0 g, 15.7 mmol). The reaction mixture was flushed with nitrogen, heated at 120°C for 2 hr and then allowed to cool to RT. The reaction mixture was diluted with EtOAc (500 mL) and hydrochloric acid (2 M, 500 mL) and the resulting suspension was filtered. The filtrate was extracted with hydrochloric acid (2 M, 2 x 500 mL). The combined aqueous extracts were basified with a saturated aqueous solution of sodium carbonate to pH 10. The precipitate formed was filtered and the filtrate was extracted with EtOAc (3 x 1 L). The combined organic extracts were dried, filtered and the solvent removed *in vacuo* to afford a grey solid. All solid materials generated during the workup procedure were combined and triturated with DCM to afford 3-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenol (**5**) (6.04 g, 84%) as a grey solid: m/z 228 $(M+H)^+$ (ES^+).

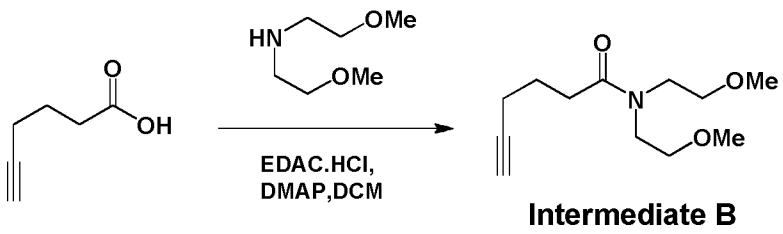
To a stirred solution of the phenol (**5**) (4.69 g, 20.66 mmol) and imidazole (2.10 g, 30.99 mmol) in dry DMF (100 mL) was added TBDMSCl (4.70 g, 30.99 mmol). After 16 hr, further aliquots of imidazole (2.10 g, 30.99 mmol) and TBDMSCl (4.70 g, 30.99 mmol) were added and the mixture was stirred for 48 hr. The reaction mixture was diluted with water (120 mL) and extracted with DCM (2 x 200 mL). The combined organic extracts were washed with water (2 x 200 mL), dried, filtered and the volume reduced to approximately 100 mL by evaporation *in vacuo*. The resulting slurry was filtered and the solid washed with heptane (50 mL) to afford the title compound (**6**) (6.05 g, 85%) as an off-white solid: m/z 343 $(M+H)^+$ (ES^+).

***Intermediate A**: 2-((4-Amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-bromo-3-(2-chlorobenzyl)quinazolin-4(3H)-one.*



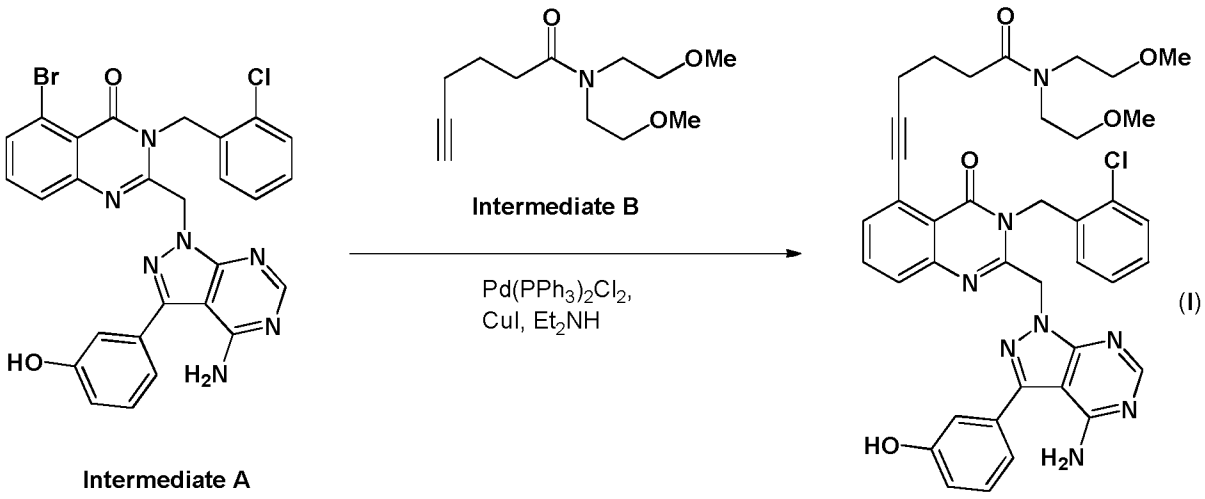
To a stirred mixture of 5-bromo-3-(2-chlorobenzyl)-2-(chloromethyl)quinazolin-4(3*H*)-one (**2**) (100 mg, 0.25 mmol) and potassium carbonate (42 mg, 0.30 mmol) in DMF (2.5 mL) was added a solution of 3-(3-(tert-butyldimethylsilyloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**6**) (94 mg, 0.28 mmol) in DMF (2.5mL) and the reaction mixture was stirred at RT for 18 hr. Potassium carbonate (3 x 35 mg, 0.75 mmol) was added in three portions over 30 hr. after which the solvent was removed *in vacuo* and the crude material was purified by flash column chromatography, eluting with 4.5% methanol in DCM, to afford the title compound, **Intermediate A**, (94 mg, 64%) as a off-white solid: R^t 2.01 min; m/z 588/590 $(M+H)^+$, (ES^+).

***Intermediate B**: N,N-bis(2-Methoxyethyl)hex-5-ynamide.*



To a solution of hex-5-ynoic acid (7.11 g, 63.4 mmol), EDC.HCl (14.0 g, 72.9 mmol) and DMAP (387 mg, 3.17 mmol) in DCM (600 mL) at 0°C was added *bis*(2-methoxyethyl)amine (9.3 mL, 63 mmol). The resulting mixture was warmed to RT for 20 hr and was then washed with hydrochloric acid (1 M, 2 x 500 mL) and with water (500 mL). The organic layer was dried and was evaporated *in vacuo* to afford the title compound, **Intermediate B**, as a yellow oil (16 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88 (3H, m), 2.26 (2H, m), 2.49 (2H, m), 3.32 (6H, s), 3.51 (4H, m), 3.55 (4H, m)

6-(2-((4-amino-3-(3-hydroxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl) methyl)-3-(2-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-*N*,*N*-bis(2-methoxyethyl)hex-5-ynamide (I)



Intermediate A ((2-((4-amino-3-(3-hydroxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)-5-bromo-3-(2-chlorobenzyl)quinazolin-4(3*H*)-one (65.7 g, 1.0 eq.)), copper(I) iodide (1.06 g, 0.05 moles/mol), bis(triphenylphosphine)palladium(II) chloride (3.92 g, 0.05 moles/mol), **Intermediate B** (N,N-bis(2-methoxyethyl)hex-5-ynamide (63.42 g, 2.5 moles/mol) and diethylamine (837.05 mL; 591.21 g, 7.5 L/mol) were added to a 2 L reactor and the mixture degassed with argon purging. The reaction mixture was warmed to 55 °C (reflux temperature) over 30 minutes and then stirred at 55 °C. After 2 hours the mixture was cooled to 22 °C before being concentrated *in vacuo* to produce a dark brown semi solid residue (201.0 g). The residue was then dissolved in MEK(781 mL) and water added (223 mL). After stirring strongly for 5 minutes the layers were separated and the aqueous layer discarded. The organic layer was washed with 10% w/v aqueous NH_4OAc (300 mL) and 2 % w/v aqueous NaCl (112 mL) before being partly concentrated *in vacuo* to an heterogeneous mixture in MEK (230 g). The mixture was stirred for 16 hours then filtered, and the precipitate was washed with MEK (3 x 25 mL). The resulting solid was dried at 50 °C *in vacuo* for 18 hours to give "crude" 6-(2-((4-amino-3-(3-hydroxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl) methyl)-3-(2-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-*N*,*N*-bis(2-methoxyethyl)hex-5-ynamide (compound of formula (I)) (54.13 g; 0.66 equiv; 65.97% yield).

Crude compound of formula (I) (53.5 g; 1.00 equiv), methanol (7.28 mL, 0.1 L/mol) and dichloromethane (145.53 mL, 2 L/mol) were stirred in a 250 mL reactor at 22 °C. After 4 hours the solid was filtered and washed with dichloromethane (29 mL) before being dried *in vacuo* at 40 °C for 18 hours to obtain compound of formula (I) (the title compound) (45.3 g; 0.85 equiv; 84.67% crystallization yield) as an off-white solid.

Example 2 – Preparation of Compound of formula (I) in solid crystalline anhydrous form

All reactions described within this example were carried out under a flow of nitrogen gas. Compound of formula (I) as prepared in Example 1 (14.0 g) and 1-propanol (210 mL, 15 L/kg) were added to a 400 mL crystallization vessel. The resulting heterogeneous mixture was stirred and warmed to 90 °C (with the mixture becoming homogeneous at 85 °C). Once the solution

had reached 90 °C, a metal scavenger (SiliaMetS® Thiol 0.7 g (5 %w/w)) was added and the mixture warmed to 95 °C. After stirring for 15 minutes at 95 °C the mixture was cooled to 90 °C and stirred for a further 2 hours at 90 °C. The metal scavenger was then filtered and the homogeneous filtrate was again stirred and warmed to 95 °C, before being cooled to 85 °C and stirred for 8 hours. The filtrate was then cooled over 8 hours to 20 °C and stirred for an additional 6 hours at 20 °C. The product was then filtered and washed with 1-propanol (6 mL) before being dried *in vacuo* at 50 °C for 18 hours to afford compound of formula (I) in anhydrous form(12.6 g, 90%) as a white solid.

The above method may optionally be adapted to facilitate crystallization with seeding.

Example 3 – XRPD analysis of Compound of formula (I) in solid crystalline anhydrous form

XRPD analysis of the anhydrous form of compound of formula (I) (Example 2) was undertaken using the method described in General Procedures. The resulting diffraction pattern is shown in Figure 1. The XRPD pattern showed diffraction peaks without the presence of a halo, thereby indicating that both materials are crystalline. Characteristic peaks of the forms are given below in Table 1:

Table 1 – Characteristic XRPD peaks for the anhydrous form of compound of formula (I)

XRPD peaks (± 0.2 degrees, 2-theta values)				
5.6	7.9	11.2	12.3	15.6
17.6	18.4	21.4	22.5	24.2

Example 4 - HPLC analysis of Compound of formula (I) in solid crystalline anhydrous form (micronized) with lactose

The chemical compatibility of the solid crystalline anhydrous form of compound of formula (I) (micronized) in combination with lactose was determined by HPLC analysis.

Micronized anhydrous form of compound of formula (I) was prepared using a jet mill micronization device (1.5 bar) (manufactured by Hosokawa Alpine) to produce the following particle size distribution: D10 = 1.40 µm; D50 = 2.77 µm and D90 = 5.29 µm (the particle size distribution was determined using laser diffraction (Malvern Mastersizer instrument).

The test batch was taken from stock containing 3.519 mg anhydrous form of compound of formula (I) (micronized) and 6006.64 mg Lactohale200.

The mixtures were analysed by HPLC at time zero and after different conditions of storage. Samples were stored under the following conditions: (i) 1, 2, 3 and 4 weeks at 50°C (ii) 1 week at 80°C (iii) 1, 2, 3 and 4 weeks at 40°C / 75% RH.

The data shown in Table 2 indicate that significant degradation was observed after storage for 1 week at 80°C and degradation was also observed after storage for 4 weeks at 50°C. These results suggest that the anhydrous form (micronized) of compound of formula (I) is not chemically stable in combination with lactose, therefore the two components would not be compatible in a pharmaceutical formulation.

The peak at RRT 0.86 has been attributed to the hydrated derivative(s) D019328 shown above.

Table 2 – stability data for the anhydrous form of the compound of formula (I) (micronized) with lactose

Conditions	RRT* 0.80	RRT* 0.86	RRT* 0.97	RRT* 1.14	RRT* 1.32
T = zero	0.21	0.12		0.12	0.13
1 week 50°C	0.17	0.23		0.10	0.12
1 week 80°C	0.52	2.53	0.78	0.19	0.12
1 week 40°C/75%RH	0.19	0.12		0.11	0.13
2 weeks 50°C	0.19	0.30		0.12	0.13
2 weeks 40°C/75%RH	0.17	0.11		0.12	0.13
3 weeks 50°C	0.19	0.38		0.12	0.14
3 weeks 40°C/75%RH	0.19	0.08		0.11	0.14
4 weeks 50°C	0.19	0.54		0.11	0.13
4 weeks 40°C/75%RH	0.18	0.20		0.11	0.14

*Area % by HPLC at the RRT indicated. Compound of formula (I) has RRT = 1.0

Example 5 – XRPD/IR analysis of Compound of formula (I) in solid crystalline anhydrous form with lactose and magnesium stearate

A mixture of the solid crystalline anhydrous form (micronized) of compound of formula (I) with lactose was prepared with the addition of 1% magnesium stearate (micronization of compound of formula (I) as described in Example 4).

Blend preparation: about 500mg of Lactohale200® and about 10mg magnesium stearate were added to an agate mortar before being mixed using a pestle and plastic blade (Feton) for 5 minutes. About 500 mg of anhydrous compound of formula (I) (micronized) was added to the mixture and the blend was mixed for a further 5 minutes.

The mixtures were stored under different temperatures and humidities and were analysed by XRPD and IR at time zero and after 1 week and 4 weeks of storage. The conditions for 1 week storage were: 40°C/75%RH open; 1 week 50°C closed; and 1 week 80°C closed. The conditions for 4 week stability storage were: 4 weeks 50°C closed; 4 weeks 40°C/75%RH open.

The IR spectrum acquired at time zero is shown in Figure 2. IR spectra were prepared for samples in the stability studies. No differences were observed between the IR spectra of the 1 and 4 week stability samples and the IR spectrum at time zero. No interaction between the anhydrous form; lactose and magnesium stearate was observed and the anhydrous form remained stable under all storage conditions.

The XRPD spectrum acquired at time zero is shown in Figure 3. XRPD spectra were prepared for samples in the stability studies. The generated XRPD patterns of the 1 and 4 week stability samples were similar to the diffraction pattern at time zero. It was clearly evident that the typical diffraction peaks of the anhydrous form did not change in the presence of Lactohale200® and magnesium stearate, indicating that the anhydrous form is physically stable in the presence of lactose and magnesium stearate.

The IR spectra showed no interaction between the anhydrous form, the lactose and the magnesium stearate, and the XRPD results showed that there was no solid state conversion of the anhydrous form. As a result, it may be concluded that the anhydrous form is physically compatible with lactose and magnesium stearate.

Example 6 - HPLC analysis of Compound of formula (I) in anhydrous form with lactose and magnesium stearate

The chemical compatibility of the solid crystalline anhydrous form (micronized) of compound of formula (I) in combination with lactose and 1% magnesium stearate was determined by HPLC analysis (micronization of compound of formula (I) as described in Example 4).

The test batch was taken from stock containing 3.704 mg anhydrous form of compound of formula (I) (micronized), 6017.90 mg Lactohale200 and 67.33 mg magnesium stearate.

The data shown in Table 3 indicate a significant increase in chemical stability compared with the same composition with the absence of magnesium stearate (see Table 2), as evidenced by only a small amount of degradation observed after storage for 1 week at 80°C (see e.g. RRT 0.86, 0.28%). These results suggest that the chemical stability of the anhydrous form (micronized) of compound of formula (I) with lactose is significantly improved by the addition of magnesium stearate to the composition. As such, the addition of magnesium stearate improves the chemical compatibility of the anhydrous form (micronized) of compound of formula (I) in combination with lactose such that they could be compatible in a pharmaceutical formulation.

Table 3 – stability data for the anhydrous form of the compound of formula (I) (micronized) with lactose and magnesium stearate

Conditions	RRT* 0.80	RRT* 0.86	RRT* 1.14	RRT* 1.32
T = zero	0.21	0.10	0.12	0.13
1 week 50°C	0.20	0.11	0.11	0.13
1 week 80°C	0.19	0.28	0.11	0.13
1 week 40°C/75%RH	0.20	0.11	0.11	0.13
2 weeks 50°C	0.20	0.08	0.11	0.14
2 weeks 40°C/75%RH	0.21	0.11	0.11	0.13
3 weeks 50°C	0.20	0.13	0.11	0.13
3 weeks 40°C/75%RH	0.20	0.11	0.11	0.14
4 weeks 50°C	0.19	0.12	0.11	0.14
4w 40°C/75%RH	0.20	0.10	0.10	0.13

*Area % by HPLC at the RRT indicated. Compound of formula (I) has RRT = 1.0

Example 7 - UPLC analysis of Compound of formula (I) in anhydrous form with lactose and metal salts of stearic acid

The chemical compatibility of the solid crystalline anhydrous form (micronized) of compound of formula (I) in combination with lactose and 1% metal salt of stearic acid (magnesium stearate, sodium stearate and calcium stearate) was determined by UPLC analysis (micronization of compound of formula (I) as described in Example 4).

Test samples were prepared as described in Table 4 below:

Table 4 – test samples for UPLC analysis after accelerated stability testing

Sample	solid crystalline anhydrous form (micronized) of compound (I) sample 1 / sample 2	Lactohale 200 sample 1 / sample 2	Metal salt of stearic acid sample 1 / sample 2
Drug only	0.50 mg / 0.47 mg		
Drug and lactose	0.58 mg / 0.47 mg	749.84 mg / 750.06 mg	
Drug, lactose, Mg stearate	0.46 mg / 0.51 mg	749.97 mg / 751.59 mg	7.40 mg / 7.55 mg
Drug, lactose, Ca stearate	0.49 mg / 0.45 mg	751.08 mg / 753.53 mg	7.67 mg / 7.80 mg
Drug, lactose, Na stearate	0.48 mg / 0.45 mg	750.20 mg / 750.42 mg	7.78 mg / 7.59 mg

Samples were dispensed into vials, sealed with caps and kept at 80 °C for 1 or 2 weeks.

Sample 1 was used for the 1 week studies and sample 2 was used for the 2 week studies.

Results are shown in Table 5 below:

Table 5 – results of UPLC analysis after accelerated stability testing

Sample	1 week 80 °C RRT* 0.87	1 week 80 °C RRT* 0.92	2 weeks 80 °C RRT* 0.87	2 weeks 80 °C RRT* 0.92
Drug only	0.00	0.08	0.00	0.08
Drug and lactose	0.58	0.39	1.80	0.77
Drug, lactose, Mg stearate	0.28	0.29	0.06	0.18
Drug, lactose, Ca stearate	0.11	0.19	0.17	0.19
Drug, lactose, Na stearate	0.00	0.09	0.00	0.09

*Area % by UPLC at RRT indicated. Compound of formula (I) has RRT = 1.0

Mass spectroscopy analysis indicates that the substance with RRT = 0.87 is D019493 and the substance with RRT = 0.92 is D019492 (confirmed by NMR) (see Scheme 1). The NMR resonance assignments for D019492 are given in Table 6:

Table 6 – ^{1}H NMR resonance assignments for D019492

	^{1}H NMR assignments (600 MHz, DMSO-d_6) δ ppm
D019492	1.59 (quin, *J*=7.30 Hz, 2 H) 2.20 (t, *J*=7.55 Hz, 2 H) 2.46 - 2.49 (m, 2 H) 3.18 (d, *J*=7.90 Hz, 6 H) 3.29 - 3.39 (m, 8 H) 4.23 (s, 2 H) 5.24 (s, 2 H) 5.76 (s, 2 H) 6.08 (d, *J*=7.55 Hz, 1 H) 6.75 (t, *J*=7.55 Hz, 1 H) 6.83 (dd, *J*=8.12, 1.70 Hz, 1 H) 6.90 (d, *J*=7.55 Hz, 1 H) 6.91 - 6.93 (m, 1 H) 7.01 (t, *J*=7.55 Hz, 1 H) 7.09 (d, *J*=7.55 Hz, 1 H) 7.29 (m, *J*=7.93, 7.93 Hz, 1 H) 7.32 (d, *J*=7.18 Hz, 1 H) 7.66 (d, *J*=7.93 Hz, 1 H) 7.77 - 7.82 (m, 1 H) 8.17 (s, 1 H) 9.67 (s, 1 H)

The data shown in Table 5 indicate a significant increase in chemical stability for formulations containing a metal salt of stearic acid compared with the same composition in the absence of a metal salt of stearic acid, as evidenced by a comparatively small amount of degradation observed after storage for 1 or 2 weeks at 80°C. These results suggest that the chemical stability of the anhydrous form of compound of formula (I) with lactose is significantly improved by the addition of metal salts of stearic acid to the composition. Therefore, the addition of metal salts of stearic acid improves the chemical compatibility of the anhydrous form of compound of formula (I) in combination with lactose such that they could be compatible in a pharmaceutical formulation.

Example 8 – Preparation of pharmaceutical formulations according to the invention

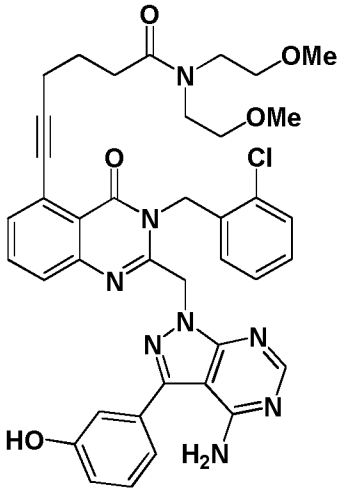
An exemplary pharmaceutical formulation of the invention consists of 0.5 wt.% of compound of formula (I) (solid crystalline anhydrous form, micronised), 98.5 wt.% lactose monohydrate (inhalation grade) and 1.0 wt.% magnesium stearate, wherein the wt.% of all components is based on the weight of the dry pharmaceutical formulation.

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, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.

Claims

1. A dry powder pharmaceutical formulation for inhalation comprising:

(i) a compound of formula (**I**)



(**I**)

that is 6-(2-((4-amino-3-(3-hydroxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl) methyl)-3-(2-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-*N*,*N*-bis(2-methoxyethyl)hex-5-ynamide or a pharmaceutically acceptable salt thereof, including all stereoisomers, tautomers and isotopic derivatives thereof and solvates thereof in particulate form as active ingredient;

(ii) particulate lactose as carrier; and

(iii) a particulate stabilizing agent selected from metal salts of stearic acid and metal salts of stearyl fumarate.

2. A pharmaceutical formulation according to claim 1, wherein the compound of formula (**I**) is in its free base form.

3. A pharmaceutical formulation according to claim 1 or claim 2, wherein the compound of formula (**I**) is in solid crystalline form.

4. A pharmaceutical formulation according to claim 3, wherein the compound of formula (**I**) is in anhydrous form.

5. A pharmaceutical formulation according to claim 4, wherein the compound of formula (I) is in solid crystalline form having the X-ray powder diffraction pattern substantially as shown in Figure 1.

6. A pharmaceutical formulation according to claim 4, wherein the compound of formula (I) is in solid crystalline form having a X-ray powder diffraction pattern containing one, two, three or four peaks selected from (± 0.2) 17.6, 18.4, 22.5 and 24.2 degrees 2-theta.

7. A pharmaceutical formulation according to any one of claims 1 to 6 wherein the active ingredient has been micronized.

8. A pharmaceutical formulation according to any one of claims 1 to 7 wherein the stabilizing agent is a metal salt of stearic acid.

9. A pharmaceutical formulation according to claim 8 wherein the stabilizing agent is magnesium stearate.

10. A pharmaceutical formulation according to any one of claims 1 to 9 wherein the lactose is α-lactose monohydrate.

11. An inhalation device comprising one or more doses of a pharmaceutical formulation according to any one of claims 1 to 10.

12. A pharmaceutical formulation according to any one of claims 1 to 10 or an inhalation device according to claim 11 for use in the treatment or prevention of a condition selected from: COPD (including chronic bronchitis and emphysema), asthma including paediatric asthma, cystic fibrosis, sarcoidosis, idiopathic pulmonary fibrosis, cachexia and inhibition of the growth and metastasis of lung tumours including non-small cell lung carcinoma.

13. Use of a pharmaceutical formulation according to any one of claims 1 to 10 in the manufacture of a medicament for the treatment or prevention of a condition selected from:
COPD (including chronic bronchitis and emphysema), asthma including paediatric asthma, cystic fibrosis, sarcoidosis, idiopathic pulmonary fibrosis, cachexia and inhibition of the growth and metastasis of lung tumours including non-small cell lung carcinoma.

14. A method of treatment of a condition selected from:
COPD (including chronic bronchitis and emphysema), asthma including paediatric asthma, cystic fibrosis, sarcoidosis, idiopathic pulmonary fibrosis, cachexia and inhibition of the growth and metastasis of lung tumours including non-small cell lung carcinoma which comprises administering to a subject an effective amount of a pharmaceutical formulation according to any one of claims 1 to 10.

15. Use of a stabilizing agent selected from metal salts of stearic acid and metal salts of stearyl fumarate in a pharmaceutical formulation containing a compound of formula (I) and lactose to increase the stability of the compound of formula (I) to chemical degradation.

16. Use according to claim 15 wherein the compound of formula (I) is in solid crystalline anhydrous form.

17. Use according to claim 16 wherein the compound of formula (I) is in solid crystalline form having the X-ray powder diffraction pattern substantially as shown in Figure 1.

18. Use according to claim 16 wherein the compound of formula (I) is in solid crystalline form having a X-ray powder diffraction pattern containing one, two, three or four peaks selected from (± 0.2) 17.6, 18.4, 22.5 and 24.2 degrees 2-theta.

19. Use according to any one of claims 15 to 18 wherein the stabilizing agent is a metal salt of stearic acid.

20. Use according to claim 19 wherein the stabilizing agent is magnesium stearate.

21. A method of increasing the stability of a pharmaceutical formulation containing a compound of formula (I) and lactose to chemical degradation which comprises including in said formulation a stabilizing amount of a stabilizing agent selected from metal salts of stearic acid such as magnesium stearate and metal salts of stearyl fumarate.

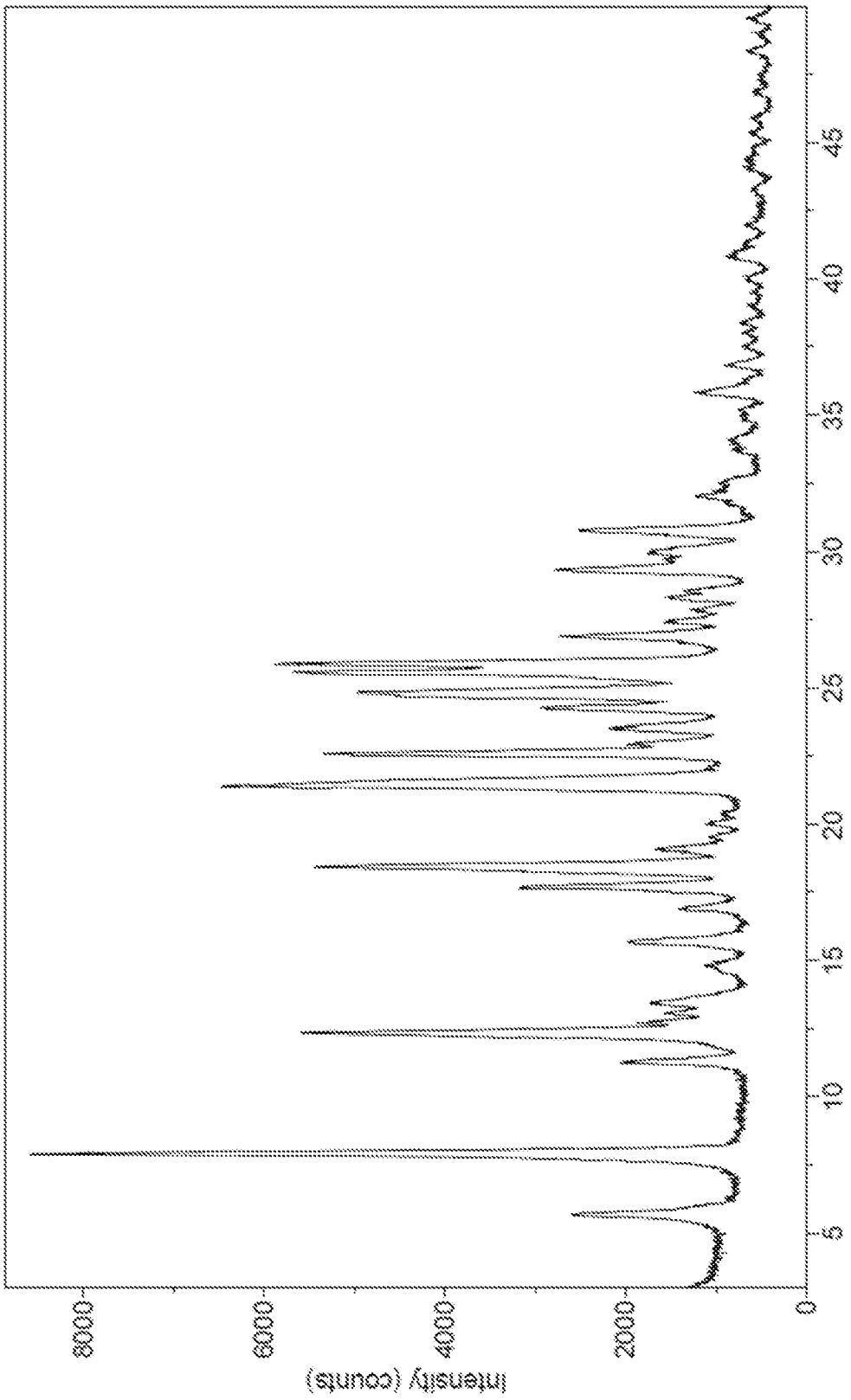
22. A method according to claim 21 wherein the compound of formula (I) is in solid crystalline anhydrous form.

23. A method according to claim 22 wherein the compound of formula (I) is in solid crystalline form having the X-ray powder diffraction pattern substantially as shown in Figure 1.

24. A method according to claim 22 wherein the compound of formula (I) is in solid crystalline form having the X-ray powder diffraction pattern containing one, two, three or four peaks selected from (± 0.2) 17.6, 18.4, 22.5 and 24.2 degrees 2-theta.

25. A method according to any one of claims 21 to 24 wherein the stabilizing agent is a metal salt of stearic acid.

26. A method according to claim 25 wherein the stabilizing agent is magnesium stearate.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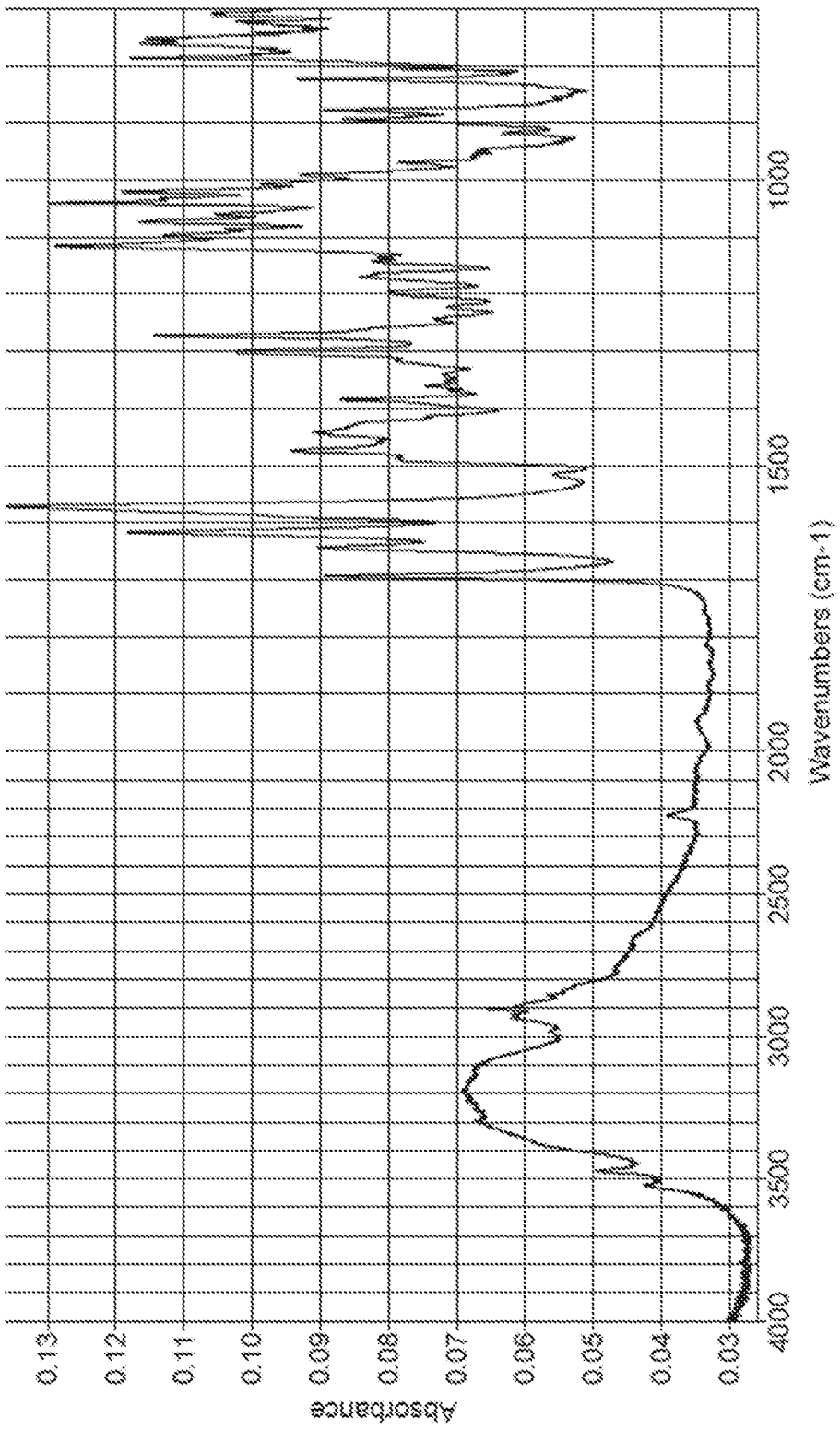
10
15
20
25
30
35
40
45
2Theta (°)

FIG. 1


Absorbance
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0.09
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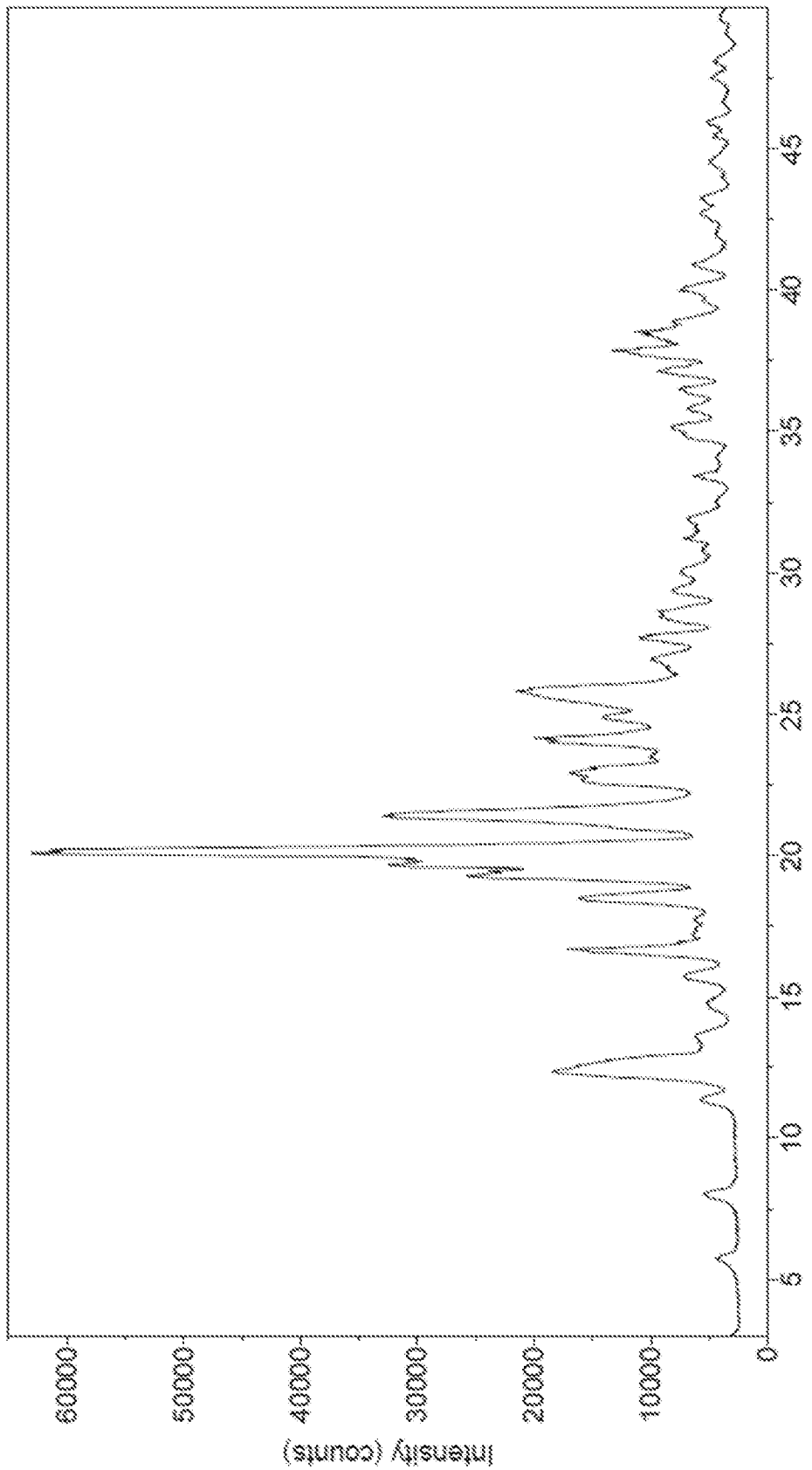
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

FIG. 2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50000
40000
30000
20000
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0
5
10
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20
25
30
35
40
45
2Theta (°)

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2013/050623

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/12 A61K9/00 A61K47/26 C07D487/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/048111 A1 (RESPIVERT LTD [GB]; KING-UNDERWOOD JOHN [GB]; ITO KAZUHIRO [GB]; MURRA) 28 April 2011 (2011-04-28) cited in the application page 34, line 30 - line 32 page 35, lines 10, 11 page 36, line 4 - line 9 page 76; compound 83 -----	1-26
A	US 7 186 401 B2 (KELLER MANFRED [DE] ET AL) 6 March 2007 (2007-03-06) cited in the application column 4, paragraphs 2, 3 the whole document -----	1-26

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2013	29/05/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Laurent, Antoine

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2013/050623

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2012/052753 A1 (RESPIVERT LTD [GB]; KING-UNDERWOOD JOHN [GB]; ITO KAZUHIRO [GB]; MURRA) 26 April 2012 (2012-04-26) cited in the application page 2, paragraph 3 page 10, paragraph 5 -----	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2013/050623

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