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(54) **Title:** 5-CHLORO-4-HYDROXY-1-METHYL-2-OXO-N-PHENYL-QUINOLINE-3-CARBOXAMIDE POTASSIUM SALT FOR TREATING INFLAMMATORY BOWEL DISEASES

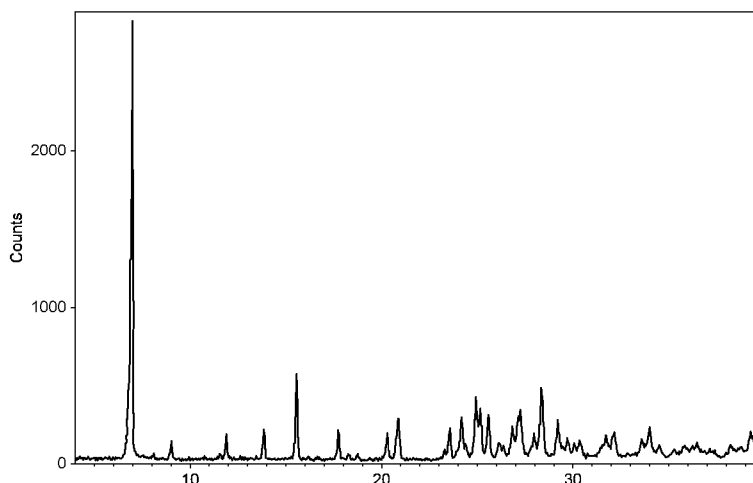
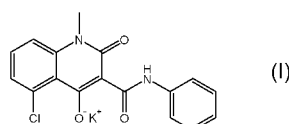


FIG. 2



(57) **Abstract:** The invention provides the compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt. It is considered to have the structure of formula (I): The compound is provided in solid (eg crystalline or amorphous) or aqueous solution form. Pharmaceutical compositions comprising the compound are also provided. The compound finds use as a medicament, in particular for the treatment or prophylaxis of an inflammatory bowel disease.



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Novel compounds

Field of the Invention

The present invention relates to the novel compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt. The compound finds
5 particular use in the treatment and/or prophylaxis of inflammatory bowel diseases.

Background of the Invention

Inflammatory Bowel Diseases (IBDs) are a heterogeneous group of diseases and disorders that are characterised by chronic inflammation of the gastrointestinal wall. Symptoms caused by the chronic inflammation include abdominal pain, diarrhoea,
10 general feeling of ill health, and loss of appetite and poor absorption of nutrients from food, which often leads to weight loss. There are two main forms of IBDs: ulcerative colitis (UC), which typically begins in the descending colon and rectum and may extend continuously to involve the entire colon (pancolitis), and Crohn's disease (CD), which most commonly involves the ileum and ascending colon. Indeterminate
15 Colitis (IC) may also be considered a form of IBD. An IBD is categorised as IC when the disease state is indistinguishable from CD and UC.

Currently-available treatments for IBDs are largely directed to the reduction of symptoms and the maintenance of remission. To prolong remission, long-term maintenance therapy is often required. First-line treatment often involves the use of
20 aminosalicylates and/or corticosteroids. Second-line treatments include immunosuppressants, Tumor Necrosis Factor (TNF) inhibitors and integrin inhibitors. Second-line treatments may be used as a monotherapy, or in combination with one or more first or second-line treatments. Often, surgical intervention is required.

Immunomodulatory drugs have also shown promise for the treatment of IBDs.
25 N-alkyl 1,2-dihydro-4-hydroxy-2-oxo-quinoline-3-carboxanilides (hereinafter referred to as N-alkyl quinoline-3-carboxanilides) are one particularly promising class of compounds that have been shown to have immunomodulatory properties. The immunomodulatory properties and therapeutic potential of N-alkyl quinoline-3-carboxanilides was first reported in the 1980s (for example, see US 4,547,511). One
30 member of this class is laquinimod, which has been reported to be beneficial for the treatment of Crohn's Disease (see for example, D'Haens et al., Gut. 2015, 64(8):1227-35, and WO 2011/014255).

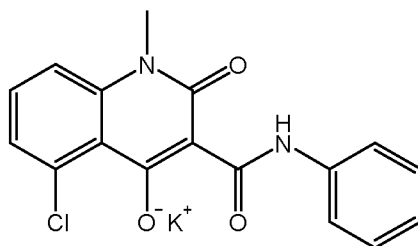
Despite initial promise, poor efficacy, toxicity and instability have limited the clinical success of N-alkyl quinoline-3-carboxanilides. For example, Jansson et al., (J. Org. Chem. 2006, 71, 1658-1667) reported that N-alkyl quinoline-3-carboxanilides are chemically reactive towards nucleophiles, making them unstable in their neutral form.

5 N-alkyl quinoline-3-carboxanilides, such as laquinimod, have also been shown to be readily metabolised by cytochrome P450 (CYPs) enzymes into various active metabolites, potentially having differing potencies, toxicities, and physicochemical properties (for example, see Tuvesson et al., 2005, Drug Metab. Dispos, 33:866–872, 2005). Notably, laquinimod was refused market authorisation in Europe for the
10 treatment of relapsing remitting multiple sclerosis due to concerns over human safety and poor efficacy (EMA 2014 Public Assessment Report - EMA/451905/2014).

Unfortunately, for many patients, available treatments for IBDs are ineffective at reducing symptoms and slowing disease progression. Many of the available treatments also cause serious adverse effects, such as an increased risk of infections,
15 inflammation of the liver, nausea and sickness, weight gain, and in rare cases progressive multifocal leukoencephalopathy. There is therefore a significant clinical need for more effective therapeutic and prophylactic treatments for IBDs. In particular, there is a need for effective treatments that provide clinical benefits for patient suffering from an IBD, whilst also displaying manageable side-effects.

20 **Summary of the Invention**

The present invention provides the compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt. The compound is considered to have the structure:



25 **Formula (I)**

The present inventors have found that the compound according to the present invention is effective for the treatment and/or prophylaxis of inflammatory bowel diseases, such as Crohn's disease and Ulcerative Colitis. Furthermore, the present

inventors have surprisingly found that the compound according to the invention has especially beneficial physical properties; beneficial properties that provide significant advantages over the free acid compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide.

- 5 For example, in solid form, the free acid 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide exists as crystals in the form of long needles and those needles visibly agglomerate. On the other hand, 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt has been found by the present inventors in solid form to be powder-like crystals with a plate-like habit. The
10 material is much easier to handle than the long needles of the free acid compound.

Further physico-chemical advantages of the 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt are described herein below.

- The efficacy of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium and its very favourable physicochemical properties allows for
15 its use in effective therapeutic treatments for reducing the symptoms of inflammatory bowel diseases, in particular Crohn's disease and Ulcerative Colitis, and prolonging disease remission.

The present invention further provides the compound of formula (I) for use as a medicament.

- 20 The present invention further provides the compound of formula (I) for use as a medicament in the treatment and/or prophylaxis of an inflammatory bowel disease.

The present invention also provides a pharmaceutical composition comprising the compound of formula (I) and at least one pharmaceutically acceptable excipient. The composition may optionally comprise one or more additional therapeutic agents.

- 25 The present invention further provides a method of treating and/or preventing an inflammatory bowel disease, said method comprising administering a pharmaceutically effective amount of the compound of formula (I) to a subject suffering from, or at risk of developing, an inflammatory bowel disease.

- Also provided herein is a use of the compound of formula (I) in the manufacture of a
30 medicament for the treatment and/or prophylaxis of an inflammatory bowel disease.

The present invention further provides a kit comprising the compound of formula (I), together with one or more pharmaceutically acceptable excipients, and optionally one or more further therapeutic agent. The kits of the present invention find use in the treatment and/or prophylaxis of inflammatory bowel diseases.

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Description of Figures

Figure 1 shows a DSC (Differential Scanning Calorimetry) trace for Example compound 1 (5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt).

10

Figure 2 shows an XRPD diffractogram for Example compound 1.

Figure 3 shows optical microscope pictures of crystals of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid (Fig 3a) and of crystals of Example compound 1 (Fig 3b).

15

Figure 4 shows the change in body weight in groups of mice after treatment with Example compound 1 in a mouse model of inflammatory bowel disease.

Figures 5 and 6 show markers of inflammation in mice treated with Example compound 1 in a mouse model of inflammatory bowel disease.

Figure 7 shows the level of Example compound 1 in the plasma at various time points in an *in vivo* pharmacokinetic study.

20

Figure 8 shows the colitis score measured in mice in a DSS model of Ulcerative Colitis using C57B1/6 mice. Mice that received 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid displayed a lower colitis score compared to mice that received vehicle only (CMC-Na, 2% w/v), or an anti-TNF α antibody.

25

Figure 9 shows the body weight change (% change from day 1 of experiment) of C57B1/6 mice in the DSS mouse model of Ulcerative Colitis. Mice that received 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid displayed reduced weight loss compared to mice that received vehicle only (CMC-Na, 2% w/v), or an anti-TNF α antibody.

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Figure 10 shows the colon length (cm) in mice in the C57B1/6 DSS mouse model of Ulcerative Colitis at Day 10 of the experiment. Mice that received 5-chloro-4-

hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid were found to have greater colon length compared to mice that received vehicle only (CMC-Na, 2% w/v), or an anti-TNF α antibody.

5 Detailed Description of the Invention

The present inventors have found that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt is effective for the treatment and/or prophylaxis of inflammatory bowel diseases, such as Crohn's disease and Ulcerative Colitis. Furthermore, the present inventors have surprisingly found that the
10 compound according to the invention has especially beneficial physical properties; beneficial properties that provide significant advantages over the free acid compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide.

Advantageous crystalline form

15 In solid form, the free acid 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide forms crystals and those crystals are long needles which are seen to agglomerate. On the other hand, 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt has been found by the present inventors in solid form to be powder-like crystals with a plate-like habit. The material is much
20 easier to handle than the long needles of the free acid compound.

5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt has been found to generally have a particle size distribution (PSD) of under 10 microns, significantly smaller than the needle length of 200-300 microns for 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid. The PSD
25 for the potassium salt is also advantageously smaller than for other salt forms; for example, both the sodium and the lithium salt were found to have PSDs of 10 to 20 microns.

The invention therefore further provides a compound of Formula (I) having D50 size in the range 0.5 to 7 μ m and a D90 size in the range 5 to 10 μ m. Preferably, the
30 compound has a D50 size in the range 2 to 5 μ m and a D90 size in the range 7 to 9 μ m.

The current inventors have further established that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt has better thermal stability than 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid. Whereas the free acid melts at 178°C and degrades at 260°C, 5-chloro-4-
5 hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt melts at 347°C and also only degrades at that temperature. The increased thermal stability brings helpful flexibility to manufacturing processes, and also allows for the compound to have a longer shelf life.

In a differential scanning calorimetry (DSC) analysis, there was no significant
10 endotherm before the melt with onset at ~ 343°C. The maximum endothermic heat flow was seen at 361.3 °C.

The invention therefore provides the compound of formula (I) in crystalline form wherein the crystalline form is characterized by a differential scanning calorimetry trace recorded at a heating rate of 10 °C per minute which shows a maximum in
15 endothermic heat flow with a peak at 361.3±2 °C.

For example, the crystalline form may be characterized by a differential scanning calorimetry trace substantially in accordance with that shown in Figure 1.

A further advantageous property of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt is it exists in a non-hydrated form and that it is
20 not hygroscopic.

A preferred solid form of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt is a crystalline salt having a powder X-ray diffractogram with characteristic peaks at $2\Theta = 6.9\pm 0.2^\circ$, $15.6\pm 0.2^\circ$, $24.9\pm 0.2^\circ$ and $28.4\pm 0.2^\circ$. The powder X-ray diffractogram may have further characteristic peaks at $2\Theta = 20.9^\circ\pm 0.2$,
25 $24.2\pm 0.2^\circ$, $25.2\pm 0.2^\circ$, $25.6\pm 0.2^\circ$ and $27.3\pm 0.2^\circ$. The powder X-ray diffractogram may have further characteristic peaks at $2\Theta = 13.9\pm 0.2^\circ$, $17.8\pm 0.2^\circ$, $23.6\pm 0.2^\circ$, $26.8\pm 0.2^\circ$, $29.2\pm 0.2^\circ$ and $34.0\pm 0.2^\circ$.

An example XRPD trace for the crystalline salt is shown in Figure 2. The invention therefore provides the compound of formula (I) in crystalline form wherein the
30 crystalline form is characterized by a powder X-ray diffraction pattern in which the

peak positions are substantially in accordance with the peak positions of the pattern shown in Figure 2.

Beneficial formation of crystalline form

5 The present inventors have surprisingly found that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt can be provided in crystalline form from a broad range of solvents. Crystals of the same type were formed when the compound was crystallised from any of ethanol, acetone, ethyl acetate, acetonitrile, THF, toluene, methanol/water 50:50 and iso-propanol/water 90:10. The fact that
10 crystals can consistently be formed from a wide variety of solvents provides helpful flexibility for manufacturing processes. Other salts that have been investigated do not display such flexibility in different solvents. For the parent free acid compound, it has been found that at least two polymorphic forms exist and that the form that is produced depends on the crystallisation solvent.

15 The invention accordingly provides a method of preparing 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt by crystallising from a solvent or solvent mixture wherein the solvent is selected from any one or more of ethanol, acetone, ethyl acetate, acetonitrile, THF, toluene, methanol/water 50:50, iso-propanol/water 90:10 and iso-propanol. Preferred solvents include ethanol, acetone,
20 ethyl acetate, acetonitrile, iso-propanol/water 90:10 and iso-propanol.

5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide may be prepared using methods known to those skilled in the art of organic chemistry. Specific methods for preparing 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide and its potassium salt according to the invention are
25 described herein in the Examples section.

Solubility in aqueous solvents

An important feature for any drug compound is its solubility in water: it determines how readily the compound can be administered in solution; it also determines how

well the compound can be absorbed into the body of the patient and distributed around the body. It thus has a significant effect on the bioavailability of the drug.

It has been found that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid has relatively low solubility. For example, in PBS (pH 7.4), 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid is so sparingly soluble as to be not quantifiable. On the other hand, the present inventors have found that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt dissolves to 0.91 μ g/ml. Similarly, in simulated colonic fluid (SCF), 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt is over twice as soluble (7.99 μ g/ml compared with 3.44 μ g/ml).

The inventors have further demonstrated in an *in vivo* study that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt is absorbed through the intestine into the plasma in rats.

This beneficial increased solubility provides an advantage to 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt in dissolved form.

A further advantageous property of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt is that it is stable in aqueous solution. It is also stable when in a slurry (beyond its solubility limit) in water.

Accordingly, the invention provides an aqueous solution comprising 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt in water. The aqueous solution may, for example, be buffered. For example, a buffered solution according to the invention may be a solution in phosphate-buffered saline (PBS). A solution according to the invention may be an aqueous pharmaceutical composition.

The compound of formula (I) may also be prepared in solid, non-crystalline form. Such forms are also known as amorphous.

Clinical efficacy:

The compound of the invention shows a surprising efficacy in treating or preventing the symptoms and development of inflammatory bowel diseases. In particular, the

present inventors have found that the compound according to formula (I) displays surprisingly beneficial properties for the treatment or prophylaxis of IBDs, such as Crohn's disease and Ulcerative Colitis.

As discussed in more detail below, the present inventors have found that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt was effective in inhibiting inflammation/edema associated with inflammatory bowel disease, as evaluated in a CD4⁺ adoptive transfer induced inflammatory bowel disease in mice. Furthermore, mice treated orally with 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt had a significant increase in CYP1A1 mRNA expression compared to untreated animals indicating that the compound is effective in activating the aryl hydrocarbon receptor (AhR) in the colon.

The inventors have further found that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide reduced weight loss and had a protective effect against the development of the clinical symptoms of Ulcerative Colitis in an *in vivo* mouse model of Ulcerative Colitis. The inventors also found that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide was effective at reducing colon shortening which indicates a reduction in edema associated with Ulcerative Colitis. The surprising efficacy of DELAQ allows for its use in effective treatment and prophylaxis of IBDs, such as Crohn's disease and Ulcerative Colitis.

The invention thus provides the compound of formula (I) for use as a medicament.

The present invention further provides the compound of formula (I) for use as a medicament in the treatment and/or prophylaxis of an inflammatory bowel disease.

The present invention further provides a method of treating and/or preventing an inflammatory bowel disease, said method comprising administering a pharmaceutically effective amount of the compound of formula (I) to a subject suffering from, or at risk of developing, an inflammatory bowel disease.

Also provided herein is a use of the compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of an inflammatory bowel disease.

N-desalkyl quinoline-3-carboxanilides have previously been reported to be active metabolites of N-alkyl quinoline-3-carboxanilides such as laquinimod and tasquinimod. In isolated form, N-desalkyl quinoline-3-carboxanilides have been reported to be unsuitable for *in vivo* administration due to poor stability and low aqueous solubility (for example, see Tuvesson et al., 2005, Drug Metab. Dispos, 33:866–872, 2005, WO 2012/050500 and Mariout et al., 2017, Tox. Appl. Pharm., 326, 54-65).

The present inventors have found that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide, and in particular 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt, is surprisingly effective at treating and preventing IBDs, in particular CD and UC, and has good stability and aqueous solubility.

Pharmaceutical compositions

While it is possible for a compound of formula (I) to be administered alone, it is preferable for it to be present in a composition and particularly in a pharmaceutical composition. Pharmaceutical compositions of the present invention comprise a compound of formula (I) and one or more pharmaceutically acceptable excipient.

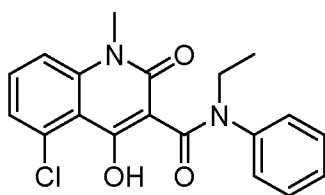
Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The compound of formula (I) may also be presented as a bolus, electuary or paste. Various pharmaceutically acceptable carriers and their formulation are described in standard formulation treatises, e.g., Remington's Pharmaceutical Sciences by E. W. Martin. See also Wang, Y. J. and Hanson, M. A., Journal of Parenteral Science and Technology, Technical Report No. 10, Supp. 42:2S, 1988.

Pharmaceutical compositions include those suitable for oral, parenteral (including subcutaneous, intradermal, intraosseous infusion, intramuscular, intravascular (bolus or infusion), and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration

although the most suitable route may depend upon for example the type of IBD that is under treatment.

Pharmaceutical compositions for rectal administration may be presented as a suppository with carriers such as cocoa butter, synthetic glyceride esters or polyethylene glycol. Such carriers are typically solid at ordinary temperatures, but
5 liquefy and/or dissolve in the rectal cavity to release the drug.

Certain compounds are known that, under suitable conditions, for example in the human body, can be converted into 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide by de-alkylation or by hydrolysis. A known compound that
10 can be converted in that way is 5-chloro-N-ethyl-4-hydroxy-1-methyl-2-oxo-N-phenyl-1,2-dihydroquinoline-3-carboxamide (known as laquinimod):



laquinimod

Preferably, compositions of the invention contain laquinimod at an amount of less than 10 mole percent (mol%) of the total combined number of moles of 5-chloro-4-
15 hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt and laquinimod present in the composition. More preferably, compositions comprising 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt contain laquinimod at amount of less than 5 mol%. For example, less than 4, 3, 2 or 1
20 mol% (for example, less than 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2 or 0.1 mol%) of laquinimod. Even more preferably, the composition of the invention is substantially free from laquinimod.

Preferably, compositions of the invention comprising 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt, contain laquinimod at an
25 amount of less than 10 wt% of the total combined mass of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt and laquinimod

present in the composition. More preferably, laquinimod is present in the composition of the invention at an amount of less than 5 wt%. For example, less than 4, 3, 2 or 1 wt% (for example, less than 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2 or 0.1 wt%) of laquinimod.

- 5 Even more preferably, the composition of the invention is substantially free from laquinimod.

The compositions of the invention may comprise one or more further therapeutic agents. Examples of further therapeutic agents that may be present in a composition of the present invention include, but not limited to, aminosalicylates (for example, 10 mesalazine, olsalazine, sulphasalazine, balsalazide), corticosteroids (for example, prednisolone, prednisone, methylprednisolone, budesonide, hydrocortisone and beclometasone dipropionate), immunosuppressants (for example, azathioprine, mercaptopurine, methotrexate, ciclosporin and tacrolimus), anti-TNF drugs (for 15 example, infliximab, adalimumab and golimumab), antibiotics (for example, ciprofloxacin and metronidazole), anti-integrin drugs (for example, vedolizumab and natalizumab), interleukin inhibitors (for example, ustekinumab) Janus Kinase inhibitors (for example, tofacitinib, filgotinib, upadacitinib, and TYK2 inhibitors such as BMS-986165).

20

Inflammatory bowel diseases

The compound of formula (I), and pharmaceutical compositions of the invention, find use in treating IBDs, for example CD and UC.

As such, the compound of formula (I) according to the invention, or composition of 25 the invention, may be administered to a subject having an IBD, such as CD or UC. The subject may be a human subject, for example a human patient.

The subject may have an IBD that may be classed as refractory, relapsed or refractory-relapsed. For example, the subject may have refractory, relapsed or refractory-relapsed CD or UC. Additionally, or alternatively, the subject may have an 30 IBD that is partially or completely resistant to established IBD treatments, such as aminosalicylates and corticosteroids. For example, the IBD may be CD or UC that is

partially or completely resistant to aminosalicylate and/or corticosteroid treatment or prophylaxis. Additionally, or alternatively, the subject may be one who has experienced, or at risk of experiencing, an adverse reaction to an established IBD treatment, such as aminosalicylates and corticosteroids.

- 5 The compound of formula (I) according to the invention, and compositions of the invention, may be administered to a subject known or suspected of being at risk of developing an IBD. For example, subjects with a known or suspected genetic predisposition for developing an IBD, such as CD or UC. For example, the compound of formula (I), or composition of the invention, may be administered to a subject in
10 need of extended remission of an IBD and/or slower progression of an IBD.

The compound of formula (I) and compositions of the invention find utility in a method of treating or preventing an IBD, said method comprising a step of administering the compound of formula (I), or a composition of the invention, to a subject having an IBD, such as CD or UC. In certain embodiments, the method of
15 treating or preventing an IBD comprises a step of administering the compound of formula (I), or a composition of the invention, to a subject known or suspected of being at risk of developing an IBD.

In certain embodiments, the method of treatment or prophylaxis comprises a step of delivering the compound of formula (I), or a pharmaceutical composition of the
20 invention, to the small and/or large intestine of a subject. For example, a step of delivering the compound of formula (I), or a pharmaceutical composition of the invention, to one or more of the duodenum, jejunum and ileum; and/or one or more of the caecum, ascending colon, transverse colon, descending colon and/or sigmoid colon. The method of treatment or prophylaxis may also comprise a step of orally or rectally
25 administering the compound of formula (I), or a composition of the invention, to a subject.

The compound of formula (I) also finds use in the manufacture of a medicament for the treatment or prophylaxis of an IBD. For example, the compound of formula (I) may be used in the manufacture of a medicament for the treatment or prophylaxis of
30 CD or UC.

Delivery to the small and/or large intestine

The composition according to the invention may be adapted for selective release of the compound of formula (I) in the small intestine or the large intestine following rectal or oral administration. For example, in certain embodiments, the compound of formula (I), or pharmaceutical composition of the invention, is administered locally to the small and/or large intestine. This may be accomplished by the use of particular coatings and/or formulations.

The compositions of the invention may have an enteric coating. Enteric coatings which protect the active ingredients in a composition from attack and degradation in the stomach, and permit release within the intestines, are known. The optimal coating for any particular formulation depends on the exact intended use, and coatings may be tailored to release the active ingredient in a particular region of the intestines, or at a particular time following ingestion.

The composition of the invention may be adapted to release the compound of formula (I) in the small intestine, for example, in one or more of the duodenum, jejunum and ileum. Additionally, or alternatively, the composition of the invention may be adapted to release the compound of formula (I) in the large intestine, for example, in one or more of the caecum, ascending colon, transverse colon, descending colon and/or sigmoid colon.

The composition of the invention may be in a solid or semi-solid form, preferably comprising an enteric coating, adapted to release the compound of formula (I) in the small intestine and/or large intestine. Such a formulation may contain one or more intermediate layers between the active ingredient and the outer enteric coating. In certain embodiments, it is possible for a composition of the invention to release a portion of its contents at one or more particular regions of the small intestine, and a further portion of its contents in one or more particular regions of the large intestine.

Dosage regimens

The amount of the compound of formula (I) which is required to achieve a therapeutic effect will vary with particular route of administration and the characteristics of the subject under treatment, for example the species, age, weight, sex, medical conditions, the particular IBD and its severity, and other relevant medical and physical factors.

An ordinarily skilled physician can readily determine and administer an effective amount of the compound of formula (I) required for treatment or prophylaxis of the IBD.

5 The compound of formula (I) may be administered daily (including several times daily), every second or third day, weekly, every second, third or fourth week or even as a high single dose depending on the subject and IBD to be treated.

Preferably, the compound of formula (I) (excluding the mass of any counterion or solvent), may be administered in an amount of about 1 to 1000 mg per administration. For example, 1, 5, 10, 15, 20, 25, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150,
10 200, 300, 400, 500, 600, 700, 800, 900 and 1000 mg.

In certain embodiments, the compound of formula (I) is administered as a composition. Preferably, the composition is a pharmaceutical composition of the present invention.

15 Whilst the compound of formula (I) may be used as the sole active ingredient in the present invention, it is also possible for it to be used in combination with one or more further therapeutic agent(s), and the use of such combinations provides one embodiment of the invention. Such further therapeutic agents may be agents useful in the treatment or prophylaxis of an IBD, or other pharmaceutically active materials. Such agents are known in the art. Examples of further therapeutic agents for use in the
20 present invention include those described herein.

The one or more further therapeutic agent(s) may be used simultaneously, sequentially or separately with/from the administration of the dosage the compound of formula (I). The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or
25 single combination forms. An ordinarily skilled physician can readily determine and administer the effective amount of one or more therapeutic agent required to have the desired therapeutic effect.

The compound of formula (I), or may be administered as an oral or rectal dosage, and thus the dosage of the compound of formula (I) must be in the form suitable for
30 delivery of the compound of formula (I) to the small and/or large intestine.

Preferred unit dosage compositions for use according to the invention are those containing an effective dose, or an appropriate fraction thereof, of the compound of formula (I). The release of the compound of formula (I) from certain composition may also be sustained, for example, if the composition contains suitable controlled-release excipients.

Kits

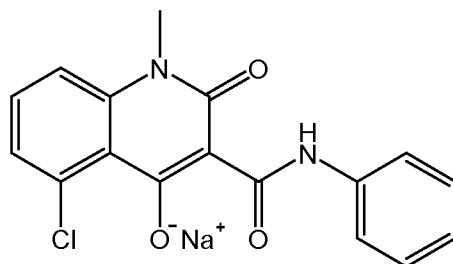
The present invention provides a kit comprising the compound of formula (I), one or more pharmaceutically acceptable excipients, and optionally one or more further therapeutic agents that are useful in the treatment or prophylaxis of an IBD. Examples of such further therapeutic agents include those described herein as being suitable for use in the present invention, and being optionally present in a pharmaceutical composition of the invention as a further therapeutic agent.

Kits of the present invention find use in the treatment and prophylaxis of an IBD, especially CD and UC.

For the avoidance of doubt, the compound of formula (I) present in a kit according to the present invention is in a form and quantity suitable for use according to the present invention. Suitable pharmaceutical compositions and formulations are described herein. The skilled person can readily determine a quantity of the compound of formula (I) suitable for including in a kit of the invention, and for use according the invention.

Further aspects of the invention

The current inventors also provide 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide sodium salt. The compound is considered to have the structure:



Formula (II)

The present inventors have found that the compound of formula (II) is effective for the treatment and/or prophylaxis of inflammatory bowel diseases, such as Crohn's disease and Ulcerative Colitis. Furthermore, the present inventors have surprisingly found that the compound of formula (II) has especially beneficial physical properties; beneficial properties that provide significant advantages over the free acid compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide.

For example, in solid form, the free acid 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide exists as crystals in the form of long needles and those needles visibly agglomerate. On the other hand, 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide sodium salt has been found by the present inventors in solid form to be powder-like crystals with a plate-like habit. The material is much easier to handle than the long needles of the free acid compound.

Further physico-chemical advantages of the 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide sodium salt are described herein below.

The efficacy of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide sodium and its favourable physicochemical properties allows for its use in effective therapeutic treatments for reducing the symptoms of inflammatory bowel diseases, in particular Crohn's disease and Ulcerative Colitis, and prolonging disease remission.

The present invention further provides the compound of formula (II) for use as a medicament.

The present invention further provides the compound of formula (II) for use as a medicament in the treatment and/or prophylaxis of an inflammatory bowel disease.

The present invention also provides a pharmaceutical composition comprising the compound of formula (II) and at least one pharmaceutically acceptable excipient. The composition may optionally comprise one or more additional therapeutic agents.

5 The present invention further provides a method of treating and/or preventing an inflammatory bowel disease, said method comprising administering a pharmaceutically effective amount of the compound of formula (II) to a subject suffering from, or at risk of developing, an inflammatory bowel disease.

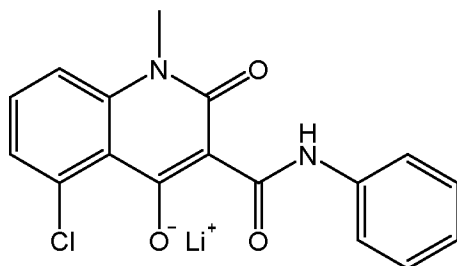
Also provided herein is a use of the compound of formula (II) in the manufacture of a medicament for the treatment and/or prophylaxis of an inflammatory bowel disease.

10 The present invention further provides a kit comprising the compound of formula (II), together with one or more pharmaceutically acceptable excipient, and optionally one or more further therapeutic agent. The kits of the present invention find use in the treatment and/or prophylaxis of inflammatory bowel diseases.

The current inventors have established that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide sodium salt has better thermal stability than 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid. Whereas the free acid melts at 178°C and degrades at 260°C, 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide sodium salt melts at 356°C and also only degrades at around 350°C. The increased thermal stability brings helpful
20 flexibility to manufacturing processes, and also allows for the compound to have a longer shelf life.

A preferred solid form of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide sodium salt is a crystalline salt having a powder X-ray diffractogram with characteristic peaks at $2\Theta = 7.2\pm 0.2^\circ$, $24.5\pm 0.2^\circ$, $26.4\pm 0.2^\circ$ and $26.5\pm 0.2^\circ$. The
25 powder X-ray diffractogram may have further characteristic peaks at $2\Theta = 9.3\pm 0.2^\circ$, $15.9\pm 0.2^\circ$, $23.1\pm 0.2^\circ$ and $25.2\pm 0.2^\circ$. The powder X-ray diffractogram may have further characteristic peaks at $2\Theta = 12.2\pm 0.2^\circ$, $18.9\pm 0.2^\circ$, $22.2\pm 0.2^\circ$ and $29.7\pm 0.2^\circ$.

The current inventors also provide 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide lithium salt. The compound is considered to have the
30 structure:



Formula (III)

The present inventors have found that the compound of formula (III) is effective for the treatment and/or prophylaxis of inflammatory bowel diseases, such as Crohn's disease and Ulcerative Colitis. Furthermore, the present inventors have surprisingly found that the compound of formula (III) has especially beneficial physical properties; beneficial properties that provide significant advantages over the free acid compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide.

For example, in solid form, the free acid 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide exists as crystals in the form of long needles and those needles visibly agglomerate. On the other hand, 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide lithium salt has been found by the present inventors in solid form to be powder-like crystals with a plate-like habit. The material is much easier to handle than the long needles of the free acid compound.

Further physico-chemical advantages of the 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide lithium salt are described herein below.

The efficacy of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide lithium salt and its favourable physicochemical properties allows for its use in effective therapeutic treatments for reducing the symptoms of inflammatory bowel diseases, in particular Crohn's disease and Ulcerative Colitis, and prolonging disease remission.

The present invention further provides the compound of formula (III) for use as a medicament.

The present invention further provides the compound of formula (III) for use as a medicament in the treatment and/or prophylaxis of an inflammatory bowel disease.

The present invention also provides a pharmaceutical composition comprising the compound of formula (III) and at least one pharmaceutically acceptable excipient. The composition may optionally comprise one or more additional therapeutic agents.

5 The present invention further provides a method of treating and/or preventing an inflammatory bowel disease, said method comprising administering a pharmaceutically effective amount of the compound of formula (III) to a subject suffering from, or at risk of developing, an inflammatory bowel disease.

Also provided herein is a use of the compound of formula (III) in the manufacture of a medicament for the treatment and/or prophylaxis of an inflammatory bowel disease.

10 The present invention further provides a kit comprising the compound of formula (III), together with one or more pharmaceutically acceptable excipient, and optionally one or more further therapeutic agent. The kits of the present invention find use in the treatment and/or prophylaxis of inflammatory bowel diseases.

The current inventors have established that 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide lithium salt has better thermal stability than 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid. Whereas the free acid melts at 178°C and degrades at 260°C, 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide lithium salt melts at 362°C and also only degrades at around 360°C. The increased thermal stability brings helpful
15
20 flexibility to manufacturing processes, and also allows for the compound to have a longer shelf life.

A preferred solid form of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide lithium salt is a crystalline salt having a powder X-ray diffractogram with characteristic peaks at $2\Theta = 6.7\pm 0.2^\circ$, $21.2\pm 0.2^\circ$, $24.3\pm 0.2^\circ$ and $25.9\pm 0.2^\circ$. The
25 powder X-ray diffractogram may have further characteristic peaks at $2\Theta = 10.4\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, $27.0\pm 0.2^\circ$ and $28.6\pm 0.2^\circ$. The powder X-ray diffractogram may have further characteristic peaks at $2\Theta = 19.8\pm 0.2^\circ$, $20.0\pm 0.2^\circ$, and $30.6\pm 0.2^\circ$.

Equivalents

30 The invention has been described broadly and generically herein. Those of ordinary skill in the art will readily appreciate that all parameters, dimensions, materials, and

configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present invention. Further, each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

Incorporation by Reference

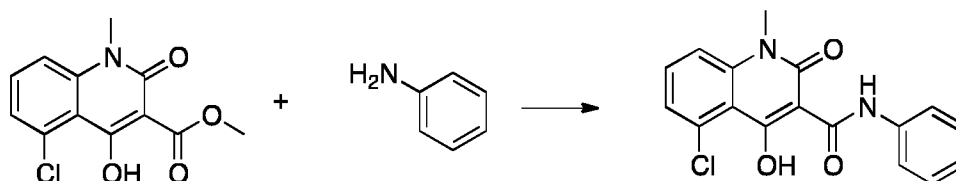
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The following Examples illustrate the invention.

Examples

Example 1: Synthesis of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt (Example compound 1)

Step a) Synthesis of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid



A mixture of methyl 5-chloro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxylate (25 g, 0.0934 mol) and aniline (17.4 g, 0.0333 mol, 2 eq) in Toluene (600 mL) were stirred at 100 °C for 17h. HPLC revealed total conversion to product. The reaction was removed from heating and the product precipitated. The reaction was left to stand at room temperature for two days. The soft solid cake was suspended in n-heptane (500 mL) and after 5 minutes of stirring the solid was filtered off. The solid was washed with a 1:1 mixture of toluene and n-heptane (1000 mL) to give crude 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide. The product was recrystallized from toluene and washed with heptane and then further purified by column chromatography (petroleum ether 100% -> DCM 100%). Final recrystallization from AcCN gave the desired product (21.5 g, 70% yield).

LC/MS: M+H=329.10. ¹H NMR (400 MHz, DMSO-d₆) δ: 12.75 (1H, s), 7.73 (1H, m), 7.65 (3H, m), 7.44 (3H, m), 7.22 (1H, m), 3.70 (s, 3H).

Step b) Preparation of potassium salt of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide

5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid (300 mg) was suspended in ethanol (6.0 mL) and 5M aqueous potassium hydroxide (0.198 mL, ~ 1.1 eq) was added. The resulting suspension was shaken well by hand and then agitated and temperature-cycled between 40°C and ambient for 48 hours.

The product was isolated by filtration, washed with ethanol (2 x 1 mL) and dried at 45°C under vacuum to constant weight. White crystals were obtained. The yield was 251 mg.

5 **Example 2: Crystallisation of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt (Example compound 1) from a variety of solvents**

5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid (20mg) was suspended in the solvent (400µL) and 5M aqueous potassium hydroxide (10 (~ 1.1eq) was added. The mixtures were shaken thoroughly by hand then temperature-cycled between ambient and 40°C for at least 18-24 hours. The solid product was isolated by filtration.

The solvents investigated were as follows.

Ethanol
Acetone
Ethyl acetate
Acetonitrile
THF
Toluene
Methanol/water 50:50
<i>Iso</i> -propanol/water 90:10

15 In each case a crystalline salt was formed. All solids were analysed by X-ray Powder Diffraction analysis (XRPD). The same polymorphic form was obtained when the salt was isolated from each of the solvents investigated.

Example 3: Characterisation of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt (Example compound 1)

a) Solution NMR

A sample of Example compound 1 was dissolved in DMSO-d₆ and analysed by ¹H NMR (400 MHz). Peaks were seen at: δ: 13.09 (1H, s), 7.65 (2H, m), 7.35 (1H, m), 7.24 (3H, m), 7.05 (1H, m), 6.81 (1H, m), 3.49 (s, 3H).

The changes in the splitting pattern compared with the free API confirmed salt formation.

10 *b) Elemental Analysis*

Elemental analysis was carried out as follows: for the determination of CHN a "Vario Micro Cube" (Elementar) was used. Chlorine content was determined using a Metrohm Model 883 Plus ion chromatograph. The potassium content was determined using an ICP-OES Model Spectro Arcos (Spectro). The analysis was carried out on 15 duplicate samples of Example Compound 1.

The results of the elemental analysis were as follows:

Atom	Predicted value	Measured value*
C	55.7%	55.3%
H	3.3%	3.4%
N	7.6%	7.5%
O	13.1%	Not measured, but calculated to 13.6%
Cl	9.7%	9.6%
K	10.7%	10.6%

* The figures presented in the table are the averages from two analytical runs.

The predicted values indicated in the table are the expected values for the mono-potassium salt with no water of hydration. As is seen in the table, the potassium 20 levels were found to be 10.6% w/w on average from the two runs. These results were

consistent with a mono potassium salt with no water of hydration. (Theoretical 10.7%).

c) Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC)

5 For the TGA analysis, approximately 5-10 mg of sample of Example Compound 1 was accurately weighed into a pierced Tzero aluminium pan and sealed with a pinhole lid using a crimper. The sample was then loaded into the chamber of a TGA thermal analyser at ambient temperature. A TA Instruments TGA5500 device was used. The sample was then heated at a rate of 20°C/min from 20°C to 400°C. The purge gas
10 used was nitrogen at a flow rate of 50cm³/min.

For the DSC analysis, approximately 2 mg of sample was accurately weighed into a pierced Tzero aluminium pan and sealed using a universal crimper. The sample was then loaded into the chamber of a DSC analyser at ambient temperature. A TA
15 Instruments DSC2500 device was used. The sample was then heated at a rate of 20°C/min from 30°C to 400°C. The purge gas used was nitrogen at a flow rate of 50cm³/min

A DSC trace for Example compound 1 is shown in Figure 1. The numerical findings were as follows. The findings for the free acid compound are shown in the third column for comparison:

	Example Compound 1	Free Acid
Solvent loss	None	~0.1%
Degradation temperature	347°C ±2°C	260°C ±2°C
Melting point	347°C ±2°C	178°C ±2°C
Enthalpy of melting	43.6J/g	91.9J/g

20

The STA data showed no sharp weight loss corresponding to an observable endotherm. A small weight loss of just under 1% at nearly 300°C may have corresponded to some moisture trapped within the structure. This indicated the sample was not hydrated or solvated however. The onset of decomposition corresponded to
25 the melt with onset at ~ 347°C. The TGA data showed a small gradual weight loss of

0.6% from the outset corresponding to surface moisture. From the DSC data, there was no significant endotherm before the melt with onset at $\sim 343^{\circ}\text{C}$. The maximum endothermic heat flow was seen at 361.3°C .

Overall, these data demonstrate that the Example compound 1 was not hydrated and had good stability up to the temperature of 347°C .

d) X-ray Powder Diffraction analysis (XRPD)

Approximately 5-10 mg of a sample of Example compound 1 was gently compressed on the XRPD zero background single obliquely cut silica sample holder. The sample was then loaded into a Philips X-Pert PRO diffractometer and analysed using the following experimental conditions:

Scan Axis	Gonio
Start Position [$^{\circ}2\theta$]	5.0084
End Position [$^{\circ}2\theta$]	49.9904
Step Size [$^{\circ}2\theta$]	0.0170
Scan Step Time [s]	1.9050
Scan Type	Continuous
PSD Mode	Scanning
PSD Length [$^{\circ}2\theta$]	2.12
Offset [$^{\circ}2\theta$]	0.0000
Divergence Slit Type	Automatic
Irradiated Length [mm]	10.00
Specimen Length [mm]	10.00
Measurement Temperature [$^{\circ}\text{C}$]	25.00
Anode Material	Cu
K-Alpha1 [\AA]	1.54060
K-Alpha2 [\AA]	1.54443
K-Beta [\AA]	1.39225
K-A2 / K-A1 Ratio	0.50000
Generator Settings	40 mA, 40 kV
Diffractometer Type	0000000011038600

Diffraction Number	0
Goniometer Radius [mm]	240.00
Dist. Focus-Diverg. Slit [mm]	100.00
Incident Beam Monochromator	No
Spinning	Yes

For certain repeat experiments, a slower scan speed was also used over a range of 4-40° 2theta as detailed below:

Scan Axis	Gonio
Start Position [°2θ]	4.0084
End Position [°2θ]	39.9804
Step Size [°2θ]	0.0170
Scan Step Time [s]	10.1600
Scan Type	Continuous
PSD Mode	Scanning
PSD Length [°2θ]	2.12
Offset [°2θ]	0.0000
Divergence Slit Type	Automatic
Irradiated Length [mm]	10.00
Specimen Length [mm]	10.00
Measurement Temperature [°C]	25.00
Anode Material	Cu
K-Alpha1 [Å]	1.54060
K-Alpha2 [Å]	1.54443
K-Beta [Å]	1.39225
K-A2 / K-A1 Ratio	0.50000
Generator Settings	40 mA, 40 kV
Diffraction Type	0000000011038600
Diffraction Number 0	
Goniometer Radius [mm]	240.00

Dist. Focus-Diverg. Slit [mm]	100.00
Incident Beam Monochromator	No
Spinning	Yes

The sample was confirmed by XRPD to be crystalline. The XRPD trace is shown in Figure 2.

The peaks in the XRPD trace were as follows:

Position (°2theta)	Height (Counts)	FWHM Left (°2theta)	D Spacing (Å)	Intensity (%)
6.9268	2878.63	0.1004	12.76158	100
9.0221	104.08	0.1004	9.80198	3.62
11.9045	139.17	0.1004	7.4343	4.83
13.8896	191.53	0.1171	6.37596	6.65
15.6065	543.42	0.1171	5.67819	18.88
17.7674	188.33	0.1004	4.99216	6.54
18.3015	30.35	0.1673	4.84767	1.05
20.3398	162.03	0.1004	4.36623	5.63
20.8979	264.57	0.1506	4.25087	9.19
23.2972	60.21	0.1004	3.81824	2.09
23.5836	200.04	0.1171	3.77253	6.95
24.1885	262.45	0.1338	3.67953	9.12
24.9349	382.33	0.1004	3.57105	13.28
25.186	312.01	0.1004	3.53602	10.84
25.591	273.31	0.1004	3.48098	9.49
26.1304	103.7	0.1673	3.41032	3.6
26.8388	205.01	0.1338	3.3219	7.12
27.2575	314.61	0.1171	3.27182	10.93
27.9818	164.25	0.1004	3.18875	5.71
28.379	457.66	0.1506	3.14502	15.9
29.2124	252.55	0.1004	3.05716	8.77
29.7516	118.42	0.1338	3.00298	4.11

30.0826	93.35	0.1004	2.97068	3.24
30.3753	105.66	0.1673	2.94272	3.67
31.7158	141.46	0.1338	2.82134	4.91
32.1597	153.11	0.2007	2.7834	5.32
33.55	109.09	0.1338	2.67117	3.79
33.9854	196.54	0.1338	2.63794	6.83
34.481	79.86	0.1673	2.60115	2.77
35.2431	46.28	0.2007	2.54663	1.61
35.8148	66.33	0.2007	2.50728	2.3
36.5031	80.53	0.4015	2.46157	2.8
38.2021	68.3	0.1338	2.35591	2.37
39.2558	139.93	0.1673	2.29507	4.86
39.5981	137	0.1338	2.27602	4.76

When a sample of Example compound 1 was stored in a slurry in water at 20mg / 400uL for 48 hours at ambient temperature, recovered, dried by evaporation and re-examined by XRPD, there was no change in the X-ray diffractogram. This indicates that the salt does not demonstrate a tendency to disproportionate.

e) Optical microscopy

Crystals of Example compound 1 were observed under an optical microscope and compared with crystals of the free acid compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide (described in Example 1a) above).

A photograph of the crystals of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide is shown in Figure 3a. The crystals are seen to be large needles of length 200-300 microns. The bar on the photograph indicates the length 100 μm .

A photograph of the crystals of Example compound 1 is shown in Figure 3b. The crystals are seen to be plate-like with a Particle Size Distribution of less than 10 microns. The bar on the photograph indicates the length 20 μm .

The free acid compound is seen to agglomerate, and this was visible with the naked eye. On the other hand, the potassium salt was found to be powder like with a plate like habit. That material is easier to handle than the long needles which made up the free acid compound.

5

f) Solubility and stability in aqueous solutions

The solubility and stability at room temperature of Example compound 1 and the free acid compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide (described in Example 1a) above) was determined in PBS (pH 7.4) and in simulated colonic fluid (SCF) at ambient temperature. The SCF was the product FaSSCoF obtained from Biorelevant.com prepared according to the manufacturer's instructions. FaSSCoF contains 0.15mM sodium cholate, 0.3mM Phospholipids, 0.1mM Oleate, 120mM sodium hydroxide, 45mM TRIS and 76mM maleate.

15 Saturated solutions were prepared in these solvents and the concentrations/impurity profile was determined by HPLC-UV using a calibration curve in the range of 1 to 150 µg/ml at 300 nm or 320 nm. Visual evaluation was also performed after every step over the testing period.

	PBS (pH7.4)	SFC
5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid	Non quantifiable	3.44 µg/ml
5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt	0.91 µg/ml	7.99 µg/ml

20 As can be seen in the table, Example compound 1 has better solubility in both of these solvents than the corresponding free acid.

The samples were also analysed for the presence of impurities. After a period of 48 and 72 hours, all impurities were below the lower limit of quantitation.

25

g) Hygroscopicity

Dynamic Vapour Sorption (DVS) analysis was carried out on a sample of Example compound 1.

5 Approximately 20 mg of sample was placed into a wire-mesh vapour sorption balance pan and loaded into an 'IgaSorp' vapour sorption balance (Hiden Analytical Instruments). The sample was then dried by maintaining a 0% humidity environment until no further weight change was recorded.

The sample was then subjected to a step profile from 0 to 90% RH at 10% RH increments. The desorption isotherm was from 90% RH to 0% RH in 10% RH steps.

10 The weight change during the sorption/desorption cycles were then monitored, allowing for the hygroscopic nature of the sample to be determined. Analysis was performed using the following parameters:

Analysis Mode F1

Wait Time 99%

15 Sample Temperature 25°C

Min Time Out 30 Mins

MaxTime Out 180 Mins

Gas Flow Rate 250 ml/min

20 The results indicated that the sample was non-hygroscopic with a small reversible weight gain of less than 0.2% when analysed to 80% RH.

Example 3: Biological activity

25 **Example 3 a): Activity of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt in inhibiting inflammation/edema associated with inflammatory bowel disease**

The efficacy of the 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt in inhibiting inflammation/edema associated with

inflammatory bowel disease was evaluated in a CD4⁺ adoptive transfer induced inflammatory bowel disease in mice.

The details of the mice were as follows:

	Species/Strain or Breed:	Fox Chase C.B-17 SCID & Balb/C
5	Vendor:	Charles River
	Age/Wt at Arrival:	CB-17 SCID – 6-7 weeks old Balb/C – 11-12 weeks old
	Gender:	Female
	Acclimation:	Acclimatization for at least 7 days after arrival
10	Housing:	5 animals/cage

On study day -1, SCID mice were weighed and evenly distributed into treatment groups based on body weight.

15 On study day 0, Balb/C mice were terminated, and spleens obtained for CD4⁺CD45RB^{high} cell isolation (Using SCID IBD Cell Separation Protocol). After cells were sorted and obtained, each animal in the treatment groups received an IP injection of CD4⁺CD45RB^{high} cells at a minimum 4×10^5 cells (200 μ l/mouse injections). A naïve group of mice was followed through the experiment without receiving the injection of cells. The naïve group comprised 5 animals.

20 On study day 21, treatment with 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt (1mg/kg, daily day 21 to 49) was initiated. The compound was formulated as a 0.1 mg/mL suspension with sodium carboxymethyl cellulose (1%, w/v). Mice received either the 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt (Example compound
25 1) or vehicle. Each of those groups comprised 10 animals.

On study day 49, animals were anesthetized with Isoflurane and bled to exsanguination followed by cervical dislocation. The entire colon was removed, measured, and weighed. The colon was analysed for its level of interferon- γ and IL-22. The results are shown in Figure 5. The inflammation in the colons was also

scored by visual and histopathological assessments. The scores are shown in Figure 6.

Each animal was weighed at 3- or 4-day intervals and the mean body weight of the mice in the three groups is shown in Figure 4. As can be seen in the figure, the mice treated with Example compound 1 had less weight loss than mice treated with vehicle only. In Figure 5, it is seen that the mice treated with Example compound 1 had lower levels of inflammatory markers than the mice treated with vehicle only. Similarly, it is seen in Figure 6 that the mice treated with Example compound 1 had fewer signs of inflammation than the mice treated with vehicle only. (* indicates a statistical significance of $p < 0.05$; ** indicates a statistical significance of $p < 0.01$). The results in Figure 5 and 6 demonstrate that Example compound 1 has a local anti-inflammatory effect in the colon of the animals.

Example 3 b): Activation of the aryl hydrocarbon receptor (AhR) in the colon of mice following administration of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt

The potential of the 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt (Example compound 1) to activate the aryl hydrocarbon receptor (AhR) in the colon following oral administration was evaluated in a wild-type (WT) mice.

The details of the mice were as follows:

Number of animals:	Order 51 (50 Study + 1 Extra)
Species/Strain or Breed:	C57Bl/6
Vendor:	Taconic
Age/Wt at Arrival:	6-7 weeks
Gender:	Female
Housing:	5 animals/cage

On study day 0, animals were weighed and evenly distributed into treatment groups based on body weight.

Also, on study day 0, treatments were initiated (a summary of the treatment schedule is shown in the table below). On study day 14, animals were asphyxiated via CO₂ inhalation followed by cervical dislocation. The entire colon was removed, collected and prepared for qPCR analysis of CYP1A1 (Normalized to GAPDH & ACTB).

Group	N ¹	Treat-Ment ²	Dose Level (mg/kg)	Dose Route ³	Regimen ⁴	Dosing Days	Dose Vol (ml/kg)	Dose Conc (mg/ml)
1	4	Naive	N/A	N/A	N/A	N/A	N/A	N/A
2	4	Ex 1	1.0 mg/kg	PO	QD	D0-13	10	0.1
3	4	Ex 1	0.1 mg/kg	PO	QD	D0-13	10	0.01
4	4	Ex 1	0.01mg/kg	PO	QD	D0-13	10	0.001

1: N, number of mice in the group.

2: Naïve mice received no test compound or vehicle. Ex 1 = Example compound 1.

10 3: PO, *per os* (oral administration).

4: QD, *quaque die* (once a day).

The Example compound 1 was formulated as a 0.1 mg/ml, 0.01 mg/ml or 0.001mg/ml suspension with sodium carboxymethyl cellulose (1%, w/v).

15 CYP1A1 qPCR results

Group	Dose (mg/kg)	Colon CYP1A1 (fold change over untreated)		Liver CYP1A1 (fold change over untreated)	
		Mean	SE	Mean	SE
2	1.0	8.34	2.75	3.44	0.30
3	0.1	7.42	2.62	2.81	0.65
4	0.01	1.03	0.34	1.08	0.34

As can be seen in the table WT mice treated with the Example compound 1 salt at 1.0 and 0.1 mg/kg had a significant increase in CYP1A1 mRNA expression compared to untreated animals indicating AhR activation. Furthermore, the results demonstrate that

the Example compound 1 has a local AhR activating effect as the increase in liver CYP1A1 expression was lower than the increase in CYP1A1 in the colon.

5 **Example 3 c): *In vivo* pharmacokinetics of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt**

An *in vivo* pharmacokinetic study in rats was performed to determine if 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt (example compound 1) can be absorbed and detected systemically after oral dosing.

10 4 male Sprague Dawley rats, approximately 225 g - 250 g at dosing were dosed with 1 mg/kg of Example compound 2 formulated as a 0.1 mg/mL suspension with sodium carboxymethyl cellulose (1%, w/v). Blood samples were taken at 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h and 24 h post dose

At each blood sampling approximately 250 μ L blood was sampled in K3EDTA vials and approximately 100 μ L plasma was also prepared.

15 The plasma samples were prepared by mixing 50 μ L plasma with 250 μ L of internal standard solution (20 ng/ml of phenacetin in ACN with 1% formic acid), mixed and centrifuged (20 min, 4000 rpm).

20 Plasma samples were transferred to Waters Ostro 96-well plate and drawn through the plate by applying 6-8 psi positive pressure for 10 min. 100 μ L of supernatant was further diluted with 50 μ L UP water and sample was submitted to analysis.

The standard and QC samples were prepared into blank rat colon homogenate and blank rat plasma. Standards were spiked into concentrations 0.1 – 10000 ng/ml of the analytes, QC samples into 3, 30, 300 and 3000 ng/ml, and were otherwise treated as samples.

25 The level of Example compound 1 in the plasma at the various time points is shown in Figure 7. It is seen that the compound is detected in the plasma and that it is rapidly cleared.

Example 3 d): Activity of 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide in an Ulcerative Colitis mouse model.

5 Ulcerative Colitis was modelled in C57Bl/6 mice by administering Dextran Sulphate Sodium (DSS) in drinking water (1.5% w/v) for 5 days. Mice were monitored daily for weight loss and clinical symptoms of disease for 10 days starting at the beginning of DSS administration.

10 Animals in different treatment groups were administered either vehicle, 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid (1 mg/kg as a 0.1 mg/mL aqueous suspension with CMC-Na (sodium carboxymethyl cellulose, 2%, w/v), or anti-TNF α antibody (anti-mouse TNF α antibody clone XT3.11). One control group of mice did not receive DSS, 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid or vehicle (herein referred to as “naïve animals”).

15 Vehicle and 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid were administered as daily administrations starting on either Day -7, though day 9. Anti-TNF α antibody was administered at 500 μ g/treatment on Days 0, 2, 4, and 6. Following termination on Day 10, colons were removed and measured. The length and weight of the colon were also assessed.

20 Compared to naïve animals, animals given DSS water developed clinical signs of disease including weight loss and diarrhoea as well as gross pathological signs of disease on experiment termination. Additionally, colon length was significantly reduced in diseased animals compared to naïve animals, while weight was increased. Shortened length and increased weight:length ratio indicates edema associated with

25 ulcerative colitis.

As shown in Figures 8 to 10, daily oral treatment with 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid (termed “Example” on Figures 8 to 10) resulted in a significant reduction in colitis clinical score on Day 9 of the study, reduced weight loss, and a significant increase in colon length on experiment

30 termination compared to vehicle-treated controls, indicating an efficacious effect of the treatment.

Example 4: 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide sodium salt (Example compound 2)

5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid (300mg) was suspended in ethanol (6.0mL) and 5M aqueous sodium hydroxide (0.198mL, ~ 1.1eq) was added. The resulting suspension was shaken well by hand and then agitated and temperature-cycled between 40°C and ambient for 48 hours.

The product was isolated by filtration, washed with ethanol (2 x 1mL) and dried at 45°C under vacuum to constant weight. White crystals were obtained. The yield was 240mg.

10 When 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide sodium salt was analysed by Thermogravimetric Analysis (TGA) using the method described in Example 3c) above, the numerical findings were as follows. The findings for the free acid compound are shown in the third column for comparison:

	Example Compound 2	Free Acid
Solvent loss	3.10%	~0.1%
Degradation temperature	350°C ±2°C	260°C ±2°C
Melting point	356°C ±2°C	178°C ±2°C
Enthalpy of melting	127.2J/g	91.9J/g

15 Approximately 5-10 mg of a sample of Example compound 2 was gently compressed on the XRPD zero background single obliquely cut silica sample holder. The sample was then loaded into a Philips X-Pert PRO diffractometer and analysed using the experimental conditions described in Example 3d) above. The sample was confirmed by XRPD to be crystalline. The peaks in the XRPD trace were as follows:

Position (°2theta)	Height (Counts)	FWHM Left (°2theta)	D Spacing (Å)	Intensity (%)
6.8328	281.87	0.1338	12.93691	14.22
7.2389	1981.62	0.1004	12.21201	100
9.2862	444.65	0.1004	9.52376	22.44
12.1652	303.67	0.1004	7.27561	15.32
12.5428	129	0.1171	7.05738	6.51

14.0265	146.8	0.1004	6.31404	7.41
14.5257	147.2	0.1171	6.09816	7.43
15.9343	482.16	0.1171	5.5621	24.33
17.8342	139.16	0.1338	4.97362	7.02
18.9295	369.42	0.1171	4.68824	18.64
20.6215	229.52	0.1338	4.30723	11.58
21.8289	147.92	0.1338	4.07164	7.46
22.2121	324.68	0.1338	4.00227	16.38
23.0972	567.42	0.1338	3.85085	28.63
24.514	1306	0.1338	3.6314	65.91
25.246	516.35	0.2007	3.52775	26.06
26.3611	650.87	0.1004	3.38101	32.85
26.5476	709.76	0.1171	3.35767	35.82
28.2156	220.44	0.3346	3.16286	11.12
28.4739	173.46	0.2007	3.13475	8.75
29.6785	370.45	0.1004	3.0102	18.69
31.2139	66.59	0.2676	2.86554	3.36
32.7791	137.02	0.1338	2.7322	6.91
33.3137	86.59	0.2007	2.68958	4.37
36.725	126.52	0.2676	2.4472	6.38
38.1042	75.91	0.4015	2.36174	3.83

When a sample of Example compound 2 was stored in a slurry in water at 20mg / 400uL for 48 hours at ambient temperature, recovered, dried by evaporation and re-examined by XRPD, there were slight changes in the X-ray diffractogram. This indicates that the salt demonstrated a tendency to disproportionate, albeit a slow tendency.

Crystals of Example compound 2 were observed under an optical microscope and compared with crystals of the free acid compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide (described in Example 1a) above).

5-Chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide sodium salt was found to be powder like with a plate like habit and a Particle Size Distribution of

less than 20 microns. The material is easier to handle than the long needles which made up the free acid compound.

The hygroscopicity of Example compound 2 was analysed using the method described above in Example 3g). The results indicated that the sample was slightly hygroscopic with a small reversible weight gain of 1% when analysed to 80% RH.

Example 5: 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide lithium salt (Example compound 3)

5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide free acid (300mg) was suspended in acetone (6.0mL) and a solution of lithium hydroxide (24mg) in water (0.2ml) was added. The resulting suspension was shaken well by hand and then agitated and temperature-cycled between 40°C and ambient for 48 hours.

The product was isolated by filtration, washed with ethanol (2 x 1mL) and dried at 45°C under vacuum to constant weight. White crystals were obtained. The yield was 225mg.

When 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide lithium salt was analysed by Thermogravimetric Analysis (TGA) using the method described in Example 3c) above, the numerical findings were as follows. The findings for the free acid compound are shown in the third column for comparison:

	Example Compound 3	Free Acid
Solvent loss	3.30%	~0.1%
Degradation temperature	360°C ±2°C	260°C ±2°C
Melting point	362°C ±2°C	178°C ±2°C
Enthalpy of melting	198.8J/g	91.9J/g

Approximately 5-10 mg of a sample of Example compound 3 was gently compressed on the XRPD zero background single obliquely cut silica sample holder. The sample was then loaded into a Philips X-Pert PRO diffractometer and analysed using the experimental conditions described in Example 3d) above. The sample was confirmed by XRPD to be crystalline. The peaks in the XRPD trace were as follows:

Position (°2theta)	Height (Counts)	FWHM Left (°2theta)	D Spacing (Å)	Intensity (%)
6.6562	15486.22	0.1004	13.27973	100
10.3703	503.93	0.1338	8.53048	3.25
12.1749	40.05	0.1338	7.26979	0.26
12.8045	57.45	0.1004	6.91373	0.37
13.2942	83.48	0.2007	6.66017	0.54
13.5732	83.31	0.1171	6.52388	0.54
14.2177	124.07	0.1004	6.22956	0.8
15.3564	302.58	0.1004	5.7701	1.95
15.8452	572.77	0.1004	5.59317	3.7
17.551	24.32	0.1004	5.05323	0.16
18.5711	269.05	0.1338	4.77789	1.74
19.0908	95.06	0.1004	4.64899	0.61
19.7568	348.64	0.1004	4.49375	2.25
20.0435	391.65	0.1004	4.43011	2.53
21.2321	911.12	0.1004	4.18471	5.88
22.1578	35.95	0.2007	4.01194	0.23
22.9311	203.45	0.1004	3.87837	1.31
23.1363	239.28	0.1004	3.84443	1.55
23.3393	158.88	0.1004	3.81146	1.03
24.3332	833.52	0.1004	3.65798	5.38
25.9287	1805.75	0.1506	3.4364	11.66
27.0238	662.61	0.1338	3.29957	4.28
27.833	120.46	0.1338	3.20545	0.78
28.6149	492.61	0.1004	3.11962	3.18
29.0144	83.12	0.1004	3.07757	0.54
30.0465	190.4	0.1171	2.97416	1.23
30.5601	368.53	0.1171	2.92535	2.38
30.9463	106.69	0.1004	2.88971	0.69
31.919	134.5	0.1338	2.80384	0.87
32.6937	87.54	0.1338	2.73915	0.57

33.3583	124.91	0.1338	2.68608	0.81
34.0206	156.78	0.1338	2.63529	1.01
35.0539	85.02	0.4015	2.55994	0.55
36.6066	124.18	0.1338	2.45484	0.8
37.709	98.6	0.2007	2.38557	0.64
39.2278	113.04	0.2342	2.29664	0.73

When a sample of Example compound 3 was stored in a slurry in water at 20mg / 400uL for 48 hours at ambient temperature, recovered, dried by evaporation and re-examined by XRPD, there were slight changes in the X-ray diffractogram. This indicates that the salt demonstrated a tendency to disproportionate, albeit a slow tendency.

Crystals of Example compound 3 were observed under an optical microscope and compared with crystals of the free acid compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide (described in Example 1a) above).

5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide lithium salt was found to be powder like with a plate like habit and a Particle Size Distribution of less than 20 microns. The material is easier to handle than the long needles which made up the free acid compound.

The hygroscopicity of Example compound 3 was analysed using the method described above in Example 3g). The results indicated that the sample was slightly hygroscopic with a small reversible weight gain of less than 0.25% when analysed to 80% RH.

Claims

1. The compound 5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-quinoline-3-carboxamide potassium salt.
2. The compound as claimed in claim 1 in solid form.
- 5 3. The compound as claimed in claim 2 in crystalline form.
4. The compound as claimed in claim 3 which is a crystalline salt having a powder X-ray diffractogram with characteristic peaks at $2\Theta = 6.9\pm 0.2^\circ$, $15.6\pm 0.2^\circ$, $24.9\pm 0.2^\circ$ and $28.4\pm 0.2^\circ$.
5. The compound as claimed in claim 4 wherein the powder X-ray diffractogram has
10 further characteristic peaks at $2\Theta = 20.9\pm 0.2$, $24.2\pm 0.2^\circ$, $25.2\pm 0.2^\circ$, $25.6\pm 0.2^\circ$ and $27.3\pm 0.2^\circ$.
6. The compound as claimed in claim 3 wherein the crystalline form is characterized by a powder X-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in Figure 2.
- 15 7. The compound as claimed in claim 3 wherein the crystalline form is characterized by a differential scanning calorimetry trace substantially in accordance with that shown in Figure 1.
8. The compound as claimed in claim 2 in amorphous form.
9. The compound as claimed in claim 1 in aqueous solution form.
- 20 10. The compound as claimed in any one of claims 1 to 9 for use as a medicament.
11. The compound as claimed in any one of claims 1 to 9 for use as a medicament for the treatment or prophylaxis of an inflammatory bowel disease.
12. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 9 and at least one pharmaceutically acceptable excipient.
- 25 13. The pharmaceutical composition as claimed in claim 12, further comprising one or more further therapeutic agents.

14. Use of the compound as claimed in any one of claims 1 to 9 in the manufacture of a medicament for the treatment or prophylaxis of an inflammatory bowel disease.

15. A method of treating or preventing an inflammatory bowel disease comprising a step of administering to a subject in need thereof a compound as claimed in any one
5 of claims 1 to 9, or the pharmaceutical composition as claimed in any one of claims 12 or 13.

16. The method as claimed in claim 15, or the use as claimed in claim 14, wherein the inflammatory bowel disease is Crohn's disease or Ulcerative Colitis.

17. The method as claimed in any one of claims 15 or 16, comprising a step of orally
10 or rectally administering the compound or the pharmaceutical composition to the subject.

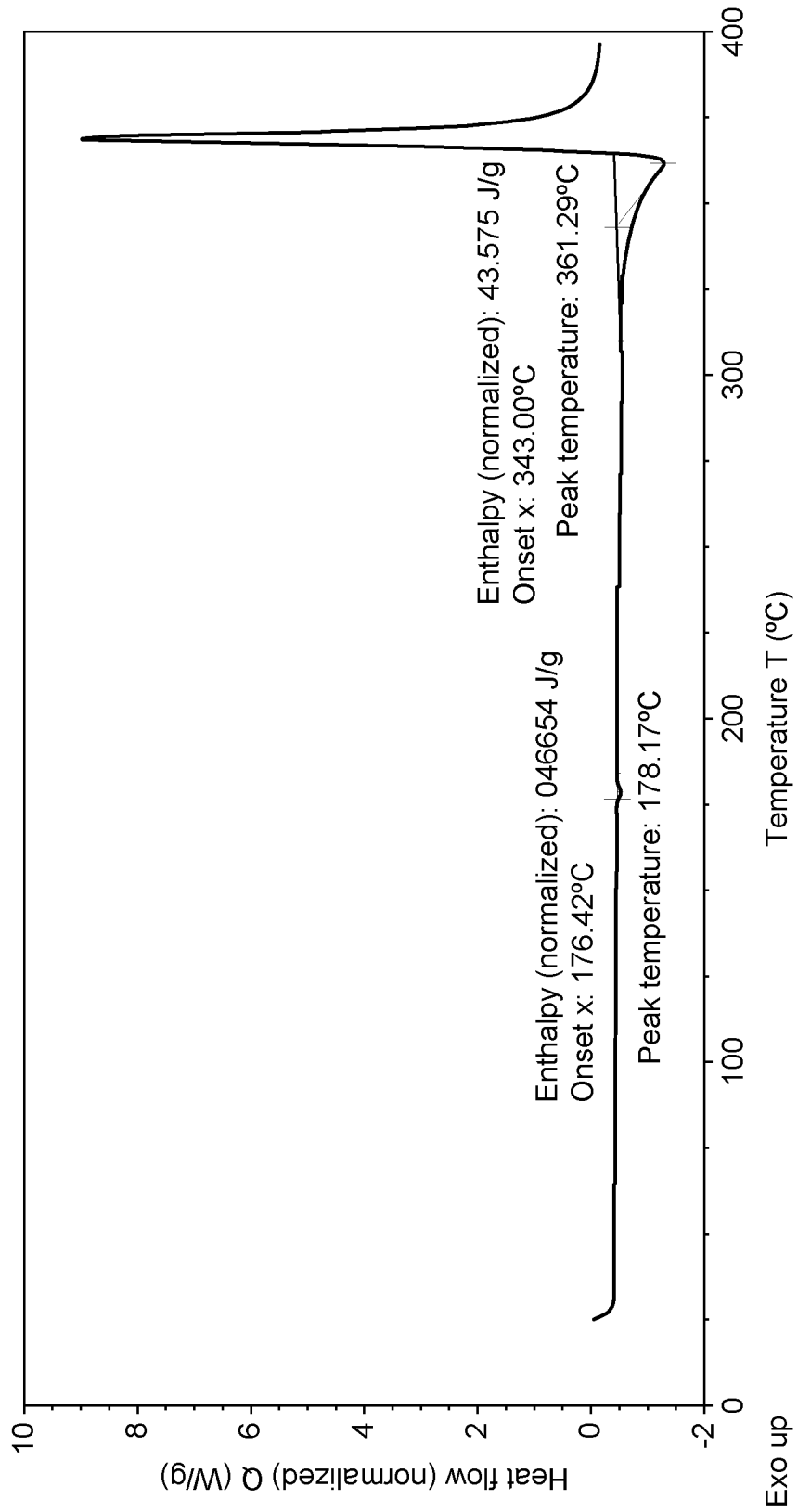


FIG. 1

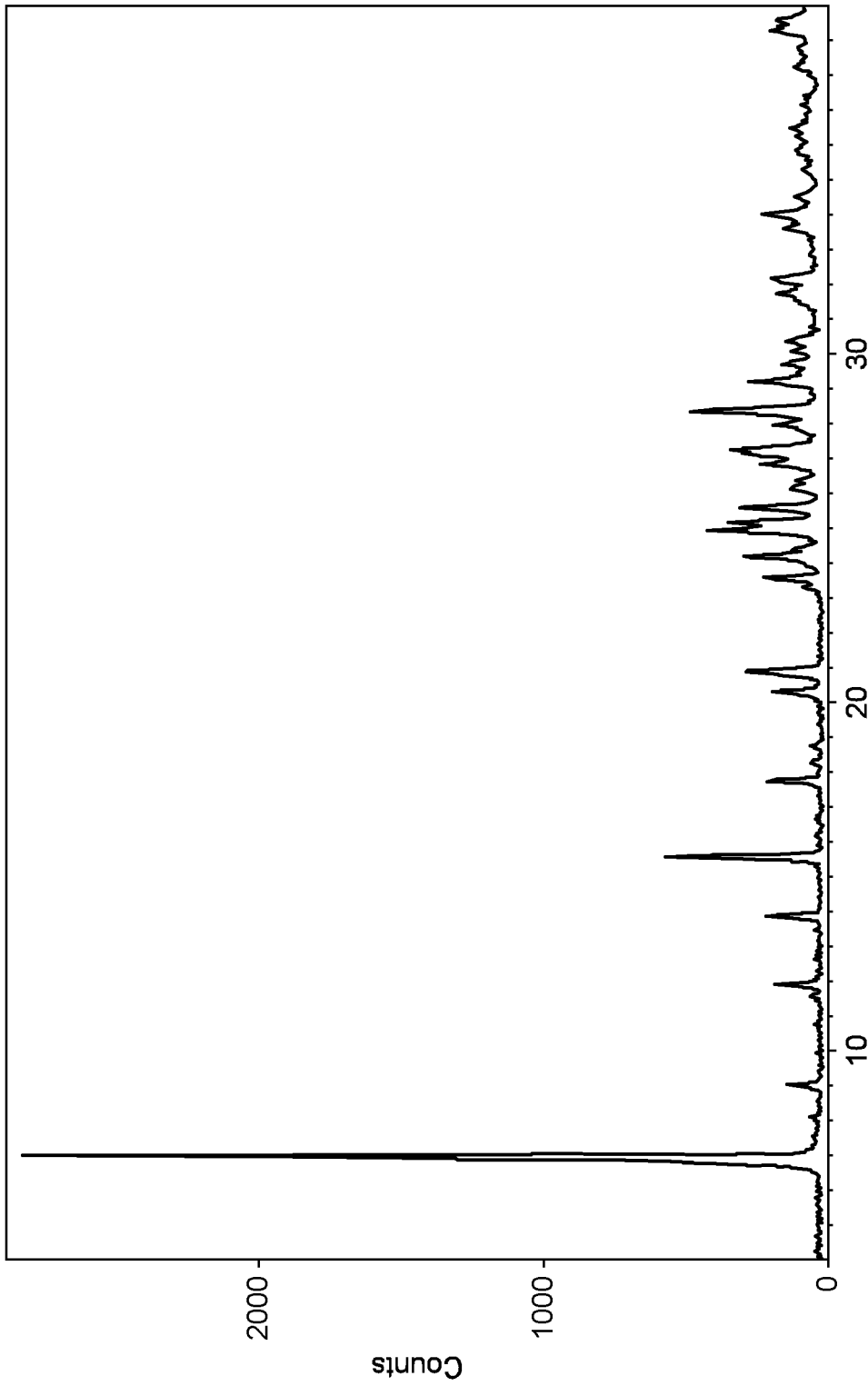
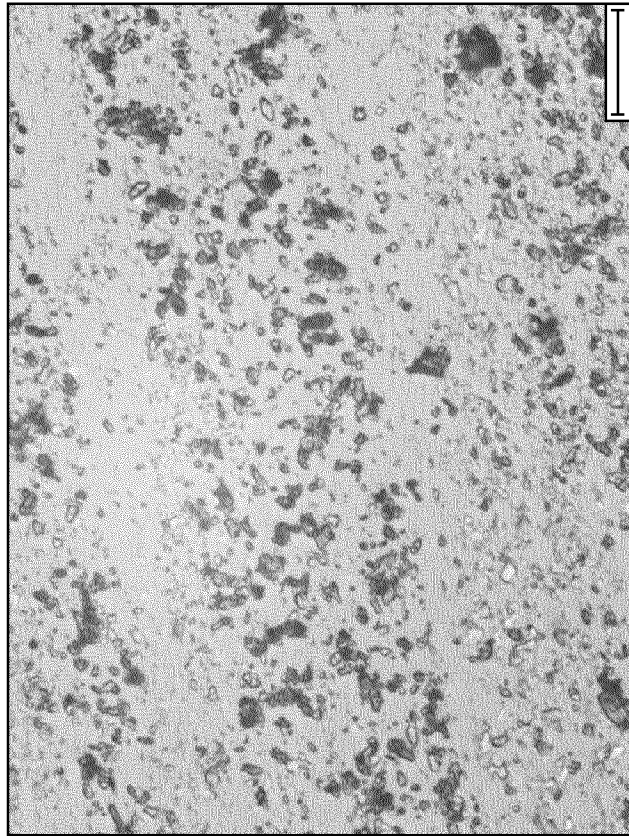
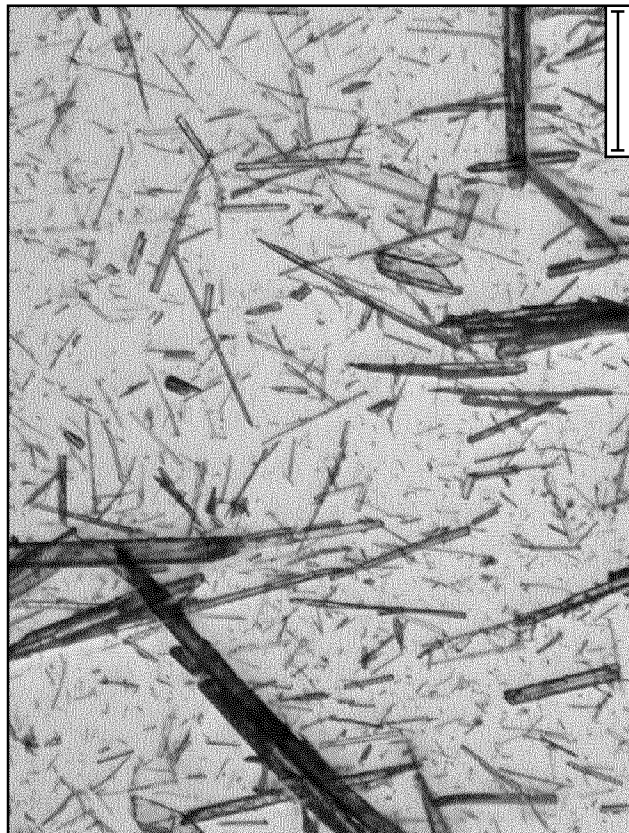


FIG. 2



b)



a)

FIG. 3

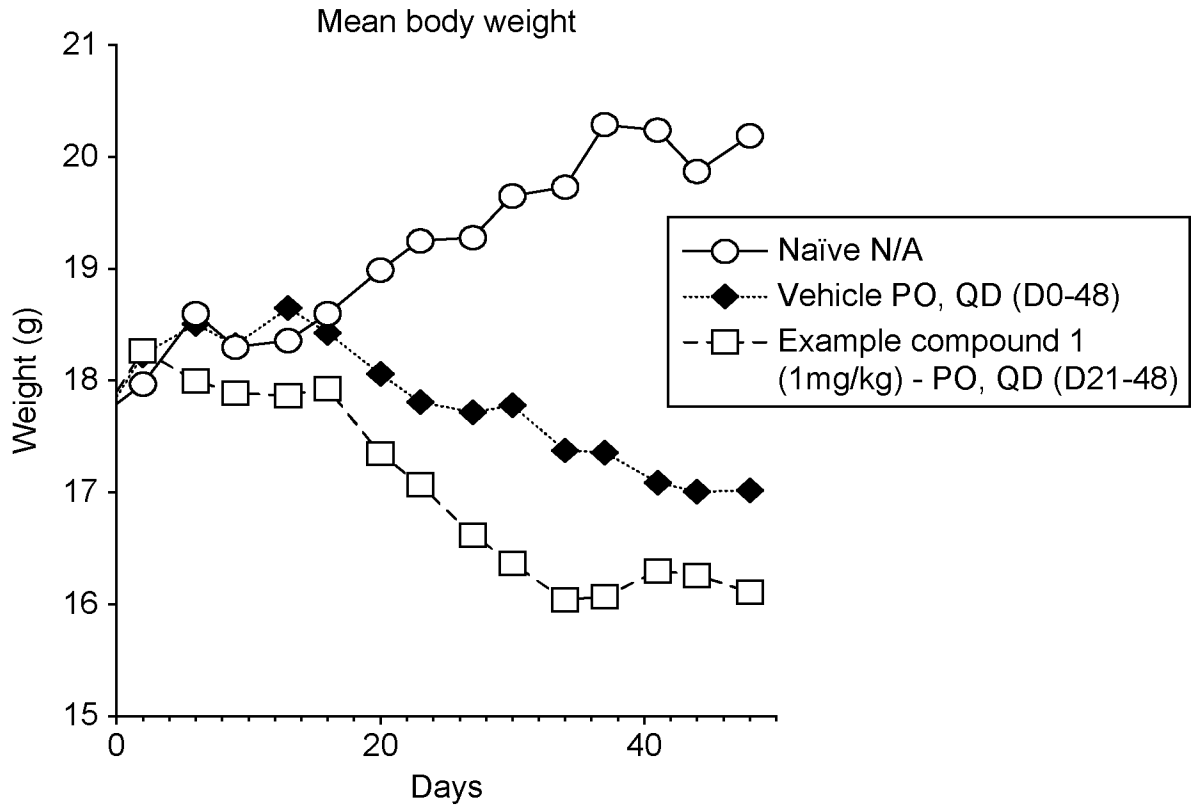


FIG. 4

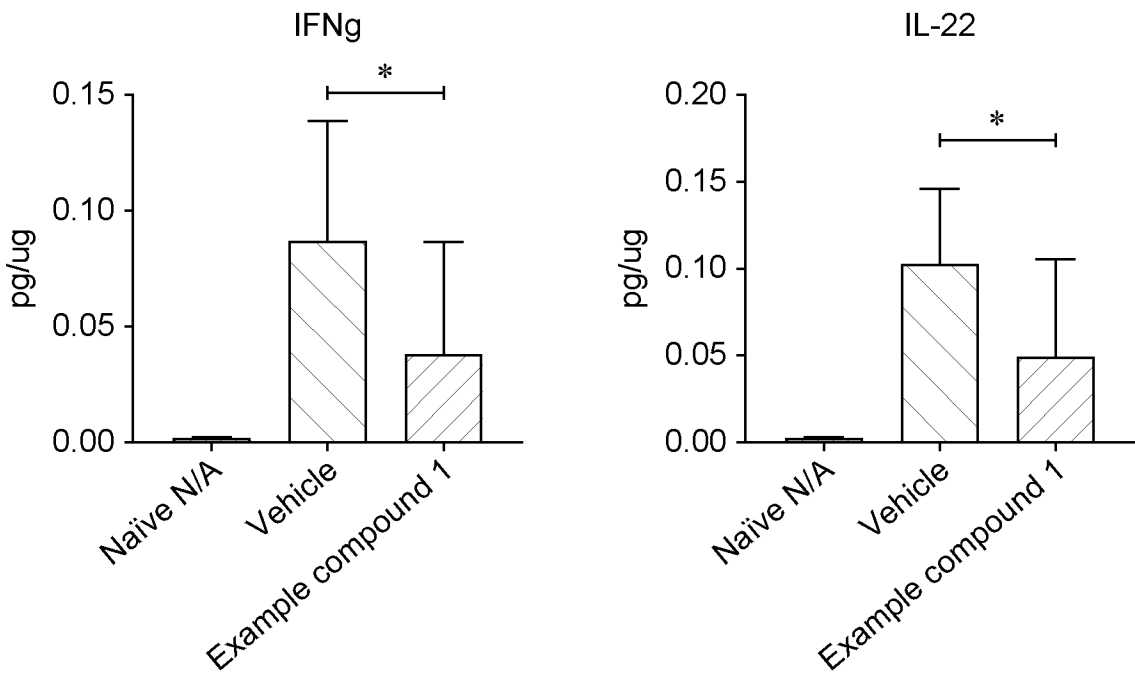


FIG. 5

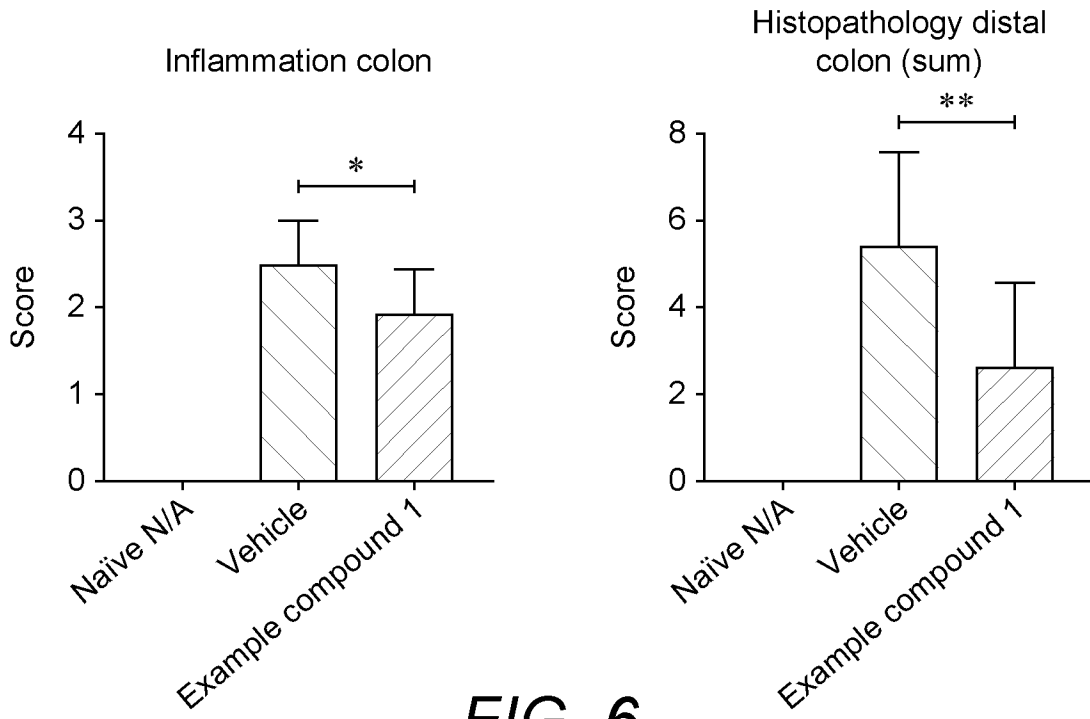


FIG. 6

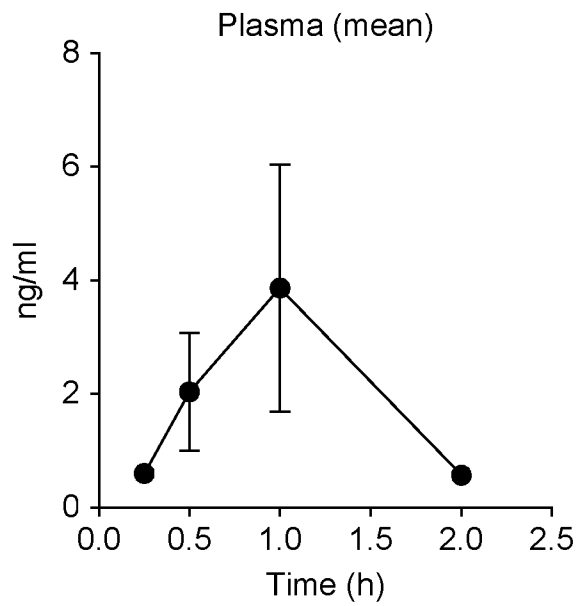


FIG. 7

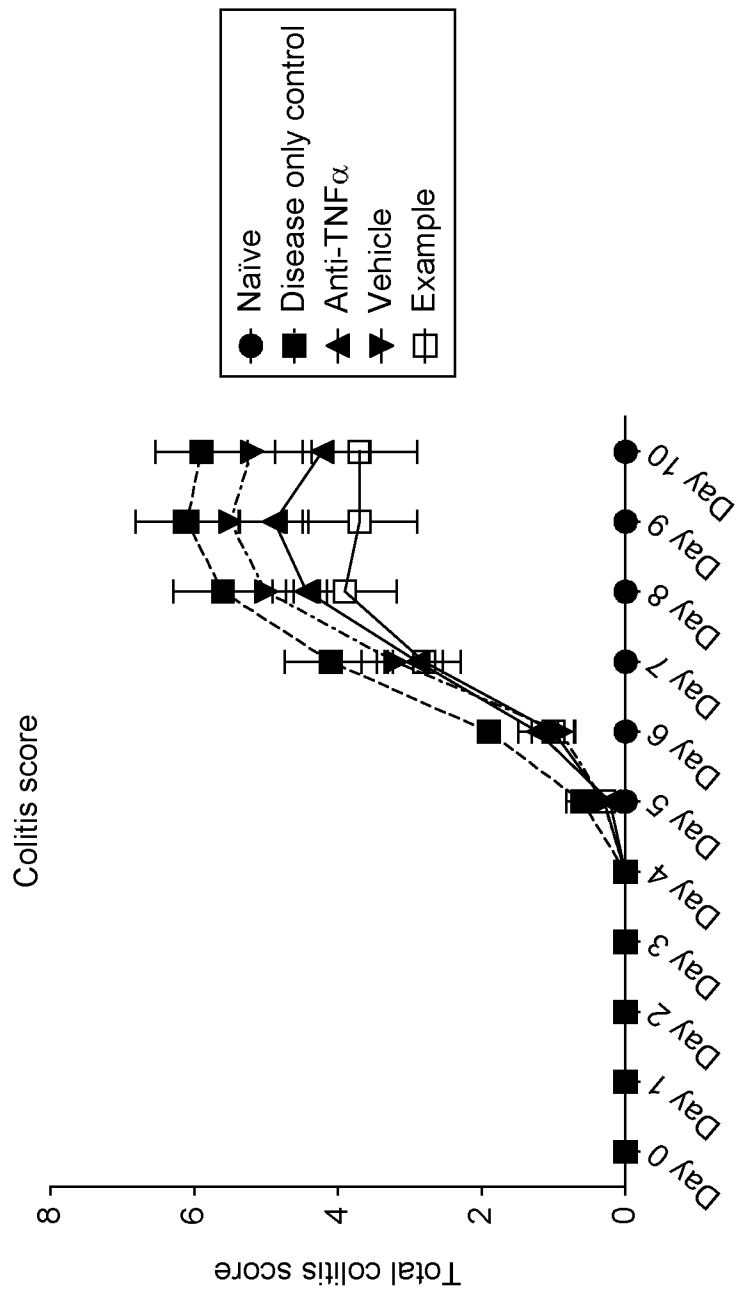


FIG. 8

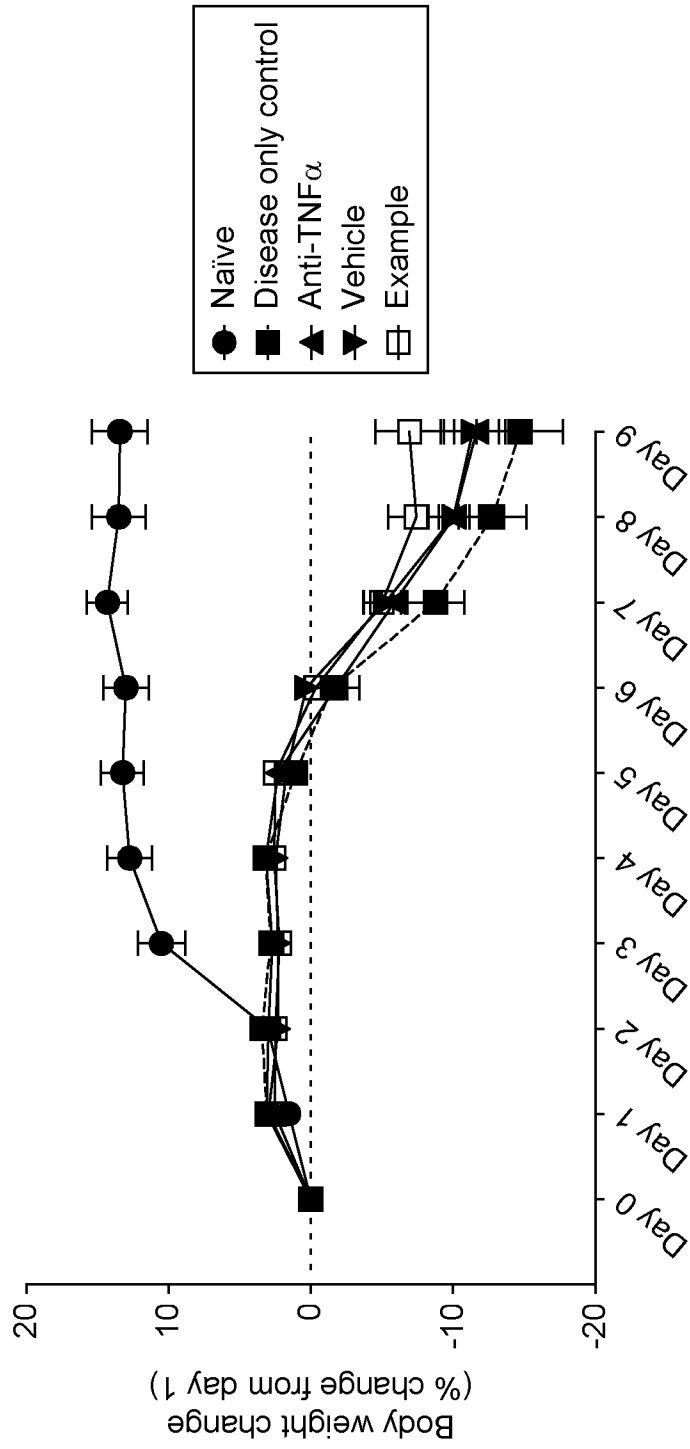


FIG. 9

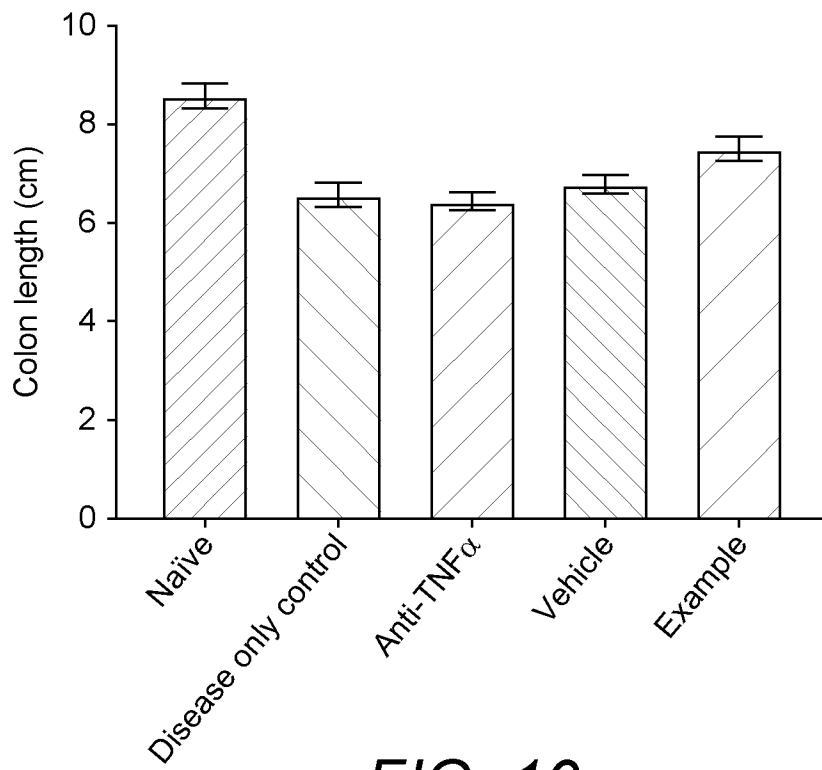


FIG. 10

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/061464

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4704 A61P1/04
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 A61P
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, 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 95/24195 A1 (PHARMACIA AB [SE]; NILSSON B0 [SE] ET AL.) 14 September 1995 (1995-09-14)	1-17
Y	page 3 claims 1,2 page 1	1-17
A	----- US 2011/027219 A1 (TARCIC NORA [IL] ET AL) 3 February 2011 (2011-02-03) see the claims	1-17
A	----- US 2012/010238 A1 (PIRYATINSKY VICTOR [IL] ET AL) 12 January 2012 (2012-01-12) page 7 ----- -/--	1-17

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance	"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
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Date of the actual completion of the international search 14 July 2021	Date of mailing of the international search report 26/07/2021
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Albayrak, Timur
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International application No

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