CRYSTALLINE SALT FORMS OF AN AZITHROMYCIN BENZOATE DERIVATIVE

The present invention relates to crystalline forms of azithromycin derivatives, and the pharmaceutical formulations and therapeutic uses thereof, specifically salts, for example, crystalline forms, of the macrolide, (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate).

Macrolides have a range of physiological activities. The majority of macrolides have an antimicrobial effect as part of their therapeutic mode of action. The macrolides are not only classified in terms of activity but also based on structure. Erythromycin, the original naturally occurring macrolide, has a 14-membered macro-lactone as a backbone. The 12-, 13-, 15- and 16-membered macrolides are mostly modified derivatives of erythromycin as well as the closely related ketolides, which are broad spectrum antimicrobials.

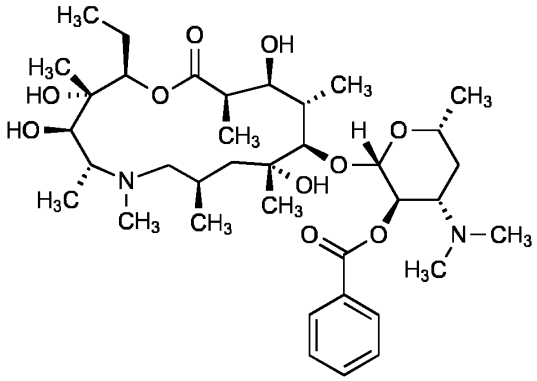
Many macrolides exhibit a range of disease modifying activities in various diseases of seemingly unrelated aetiology. In addition to antimicrobial activity, some macrolides have been proposed to possess alternative "non-antimicrobial" effects. Some of those effects have been proposed to manifest themselves in a disease modifying mode of action in humans that is primarily anti-inflammatory or immunomodulatory (Kanoh, S. and Rubin B.K., Mechanisms of Action and Clinical Application of Macrolides as Immunomodulatory Medications, *Clinical Microbiology Reviews*, 2010, **23(3)**, 590-615). The term "Immunolides" has been used to describe macrolide compounds that have selective immunomodulatory effects (see Fecik *et al.*, *Current Opinion in Drug Discovery and Development*, 2005, **8(6)**, 741-747).

Over-use of antibiotics is one of the causes of the rise of antibiotic-resistant strains of bacteria. The use of macrolides in the treatment of conditions other than bacterial infections has thus been limited by the need to avoid the unnecessary widespread use of antibiotic compounds. There is thus a clinical need for macrolide compounds with clinically useful immunomodulatory activity but sufficiently low antimicrobial activity not to constitute a resistance-promotion hazard. Despite the significant interest in the development of such immunolides, suitable compounds have not yet been developed. Certain compounds are described in WO2014/166503 as having good non-antibiotic properties but reduced antimicrobial activity. In practice the compounds described therein do not have sufficient activity to be clinically useful.

Some limited numbers of derivatives of azithromycin are known, for example from patent publications WO2006/087644, WO2004/005310, WO2004/139821, WO03/070174 and CN1837225.

A particular macrolide, is the azithromycin derivative which is the compound of Formula (I), with the chemical name, (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-

azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate), represented by the chemical structure:



This compound is disclosed in International application publication number: WO 2017/085329.

It is desirable to develop novel forms of the compound of Formula (I), such as salts, preferably crystalline salts, with improved properties. Such salts and crystalline forms may have improved properties such as in their bioavailability, stability, purity, and/or manufacturability at certain conditions that may be suitable for medical or pharmaceutical uses.

Crystalline forms of a compound of Formula (I), including substantially pure forms, may provide the advantage of bioavailability and stability, suitable for use as an active ingredient in a pharmaceutical composition. Variations in the crystal structure of a pharmaceutical drug substance or active ingredient may affect the dissolution rate (which may affect bioavailability, etc.), manufacturability (e.g., ease of handling, ability to consistently prepare doses of known strength), and stability (e.g. , thermal stability, shelf life, etc.) of a pharmaceutical drug product or active ingredient. Such variations may affect the preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solutions or solid oral dosage form including tablets and capsules. Compared to other forms such as non-crystalline or amorphous forms, crystalline forms may provide desired or suitable hygroscopicity, particle size controls, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, and/or process control. Thus, crystalline forms of a compound of Formula (I) may provide advantages such as improving: the manufacturing process of the compound, the stability or storability of a drug product form of the compound, the stability or storability of a drug substance of the compound and/or the bioavailability and/or stability of the compound as an active agent.

Therefore, there is the need to provide forms of a compound of Formula (I) with physicochemical properties which render them suitable for improved pharmaceutical formulations; in particular solid forms with a balanced profile of appropriate physicochemical properties such as suitable solubility, chemical stability, favourable morphology, improved filterability, appropriate hygroscopicity. There is, as well, the need for pharmaceutical compositions comprising the same.

Crystalline forms tend to have advantageous properties for the preparation of pharmaceutical compositions. however, the compound of Formula (I) has proved very difficult to crystallize. Surprisingly, we have been able to crystallize the compound of Formula (I) with a limited number of counter ions using specific solvents systems.

The crystalline forms of the compound Formula (I) described herein which may exhibit one or more favourable characteristics described above. The processes for the preparation of the crystalline forms described herein and characterization of these crystalline forms are described in detail below.

Therefore, according to a first embodiment of the invention there is provided a salt of the compound (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate).

According to a further embodiment of the invention there is provided a crystalline salt form of the compound (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate).

According to a further embodiment of the invention there is provided the compound (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) in crystalline form.

According to a further embodiment there is provided the compound, (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate), as a crystalline salt, for example, a crystalline pharmaceutically acceptable salt.

According to a further embodiment of the invention there is provided the compound (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) in crystalline form which is a channel hydrate.

In a further embodiment of the invention there is provided a tartrate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate), for example, a tartrate salt in crystalline form.

In a further embodiment of the invention there is provided an oxalate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate), for example, an oxalate salt in crystalline form.

In a further embodiment of the invention there is provided an Armstrong acid salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate), for example, an Armstrong acid salt in crystalline form.

In a further embodiment of the invention there is provided a naphthalenedisulfonate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate), for example, a naphthalenedisulfonate salt in crystalline form, such as a naphthalene 1,5-disulfonate salt in crystalline form.

Detailed Description

A single molecule of a compound of Formula (I) can be form a salt with up two counter ions. Therefore, salts, for example, crystalline salts, of the invention comprise hemi, mono and bis salts.

Tartrate salts of the invention

According to a further embodiment of the invention there is provided a tartrate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate).

According to a further embodiment of the invention there is provided a tartrate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate), wherein the salt is a hydrate.

According to a further embodiment of the invention there is provided a tartrate hydrate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate), wherein the hydrate is a dihydrate.

According to a further embodiment of the invention there is provided a tartrate hydrate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate), wherein the hydrate is a trihydrate.

According to a further embodiment of the invention there is provided a tartrate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) in crystalline form.

According to a further embodiment of the invention there is provided a mono tartrate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) in crystalline form.

According to a further embodiment of the invention there is provided a tartrate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) in crystalline form, comprising between 2% and 8% , for example about 5% water.

In a further embodiment the invention there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterised by an XRPD spectrum with one or more peaks on a 2-theta scale in the XRPD spectrum selected from the group comprising 5.3°, 6.5°, 8.4°, 9.3°, 10.8°, 14.3°, 15.9°, 17.2°, 18.8° and 21.9°θ ± 0.2° 2θ.

In a further embodiment there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterised by an XRPD spectrum comprising peaks at 5.3°, 6.5° and 8.4°θ ± 0.2° 2θ. In a further embodiment, there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterised by an XRPD spectrum further comprising peaks at 10.8° and 17.2°θ ± 0.2° 2θ. In a further embodiment, there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterised by an XRPD spectrum further comprising peaks at 9.3°, 14.3° and 21.9°θ ± 0.2° 2θ. In a further embodiment, there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterised by an XRPD spectrum further comprising peaks at 15.9° and 18.8°θ ± 0.2° 2θ.

In a further embodiment of the invention, there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterised by an XRPD spectrum substantially as shown in Figure 1.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterised by thermal events at about 106°C and about 148°C in a differential scanning calorimetry (DSC) thermal profile recorded at 20°C/minute.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by differential scanning calorimetry (DSC) thermal profile substantially as set forth in Figure 4a.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by two mass loses of about 7.8wt% between 25°C and 87°C, and about 3.7wt% between 90°C and 200°C as measured by thermogravimetric analysis (TGA).

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by a thermal profile substantially as set forth in Figure 4a

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterised by thermal events at about 102°C and about 112°C in a differential scanning calorimetry (DSC) thermal profile, for example, recorded at 20°C/minute.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-

tetrahydropyran-3-yl] benzoate) tartrate characterized by differential scanning calorimetry (DSC) pattern substantially as set forth in Figure 4b.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by two mass loses of about 8.7wt% between 25°C and 87°C, and about 5.6wt% between 90°C and 200°C as measured by thermogravimetric analysis (TGA).

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by a thermal profile substantially as set forth in Figure 4b

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterised by thermal events at about 108°C and about 152°C in a differential scanning calorimetry (DSC) thermal profile, for example, recorded at 20°C/minute.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by differential scanning calorimetry (DSC) pattern substantially as set forth in Figure 4c.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by two mass loses of about 3.1wt% between 25°C and 80°C, and about 2.4wt% between 80°C and 200°C as measured by thermogravimetric analysis (TGA).

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by thermal profile substantially as set forth in Figure 4c

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by two mass loses of about 8.7wt% between 25°C and 110°C, and about 1.9wt% between 110°C and 200°C as measured by thermogravimetric analysis (TGA).

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by a moisture content of about 14wt% before a first desorption, a water absorption of about 2wt% per 10% relative humidity up to 20wt% before a second desorption as measured by dynamic vapour sorption (DVS).

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by a dynamic vapor sorption (DVS) profile substantially as set forth in Figure 5a.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by a dynamic vapor sorption (DVS) profile substantially as set forth in Figure 5b.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by a melting point between 160°C to 174°C as measured by Hot Stage Microscopy.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by a melting point between 160°C to 180°C as measured by Hot Stage Microscopy.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by one or more of the parameters recited above.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by a proton NMR spectrum substantially as set forth in Figure 6a.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate characterized by a proton NMR spectrum substantially as set forth in Figure 6b.

Oxalate salts of the invention

According to one embodiment of the invention there is provided an oxalate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate).

According to one embodiment of the invention there is provided an oxalate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) in crystalline form.

In a further embodiment the invention there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) oxalate characterised by one or more peaks on a 2-theta scale in an XRPD spectrum selected from the group comprising 9.2°, 11.9°, 15.8°, 16.1°, 16.3°, 16.4°, 17.7°, 18.5°, 18.7°, and 19.6° θ ± 0.2° 2θ.

In a further embodiment there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) oxalate characterised by an XRPD spectrum comprising peaks at 9.2°, 16.1°, 16.3°, 18.7°, 19.6° θ ± 0.2° 2θ. In a further embodiment, there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-

3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) oxalate characterised by an XRPD spectrum further comprising peaks at 11.9°, 15.8°, 16.4°, 17.7°, 18.5° θ ± 0.2° 2θ.

In a further embodiment of the invention, there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) oxalate characterised by an XRPD spectrum substantially as shown in Figure 2.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) oxalate characterized by one or more of the parameters recited above.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) oxalate characterized by a proton NMR spectrum substantially as set forth in Figure 7.

Naphthalenedisulfonate salts of the invention

According to one embodiment of the invention there is provided a naphthalenedisulfonate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate).

According to one embodiment of the invention there is provided a naphthalenedisulfonate salt of (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) in crystalline form.

In a further embodiment the invention there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) naphthalenedisulfonate characterised by one or more peaks on a 2-theta scale in an XRPD spectrum selected from the group comprising 5.6°, 8.9°, 10.0°, 10.5°, 11.4°, 12.7°, 13.5°, 16.3°, 18.1° and 20.3 ° θ ± 0.2° 2θ.

In a further embodiment there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-

heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) naphthalenedisulfonate characterised by an XRPD spectrum comprising peaks at 8.9°, 10.0°, 10.5°, 12.7° and 18.1° θ ± 0.2° 2θ . In a further embodiment, there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) naphthalenedisulfonate characterised by an XRPD spectrum further comprising peaks at 5.6°, 11.4°, 13.5°, 16.3°, 20.3° θ ± 0.2° 2θ.

In a further embodiment of the invention, there is provided a crystalline solid (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) naphthalenedisulfonate characterised by an XRPD spectrum substantially as shown in Figure 3.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) naphthalenedisulfonate characterized by one or more of the parameters recited above.

According to a further embodiment of the invention there is provided (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) naphthalenedisulphonate characterized by a proton NMR spectrum substantially as set forth in Figure 8.

Pharmaceutical Compositions

For the purposes of administration, in certain embodiments, the salts described herein are administered as a raw chemical or are formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of Formula (I), and a pharmaceutically acceptable excipient. The salt of Formula (I) is present in the composition in an amount which is effective to treat a particular disease or condition of interest. The activity of compounds of Formula (I) can be determined by one skilled in the art, for example, as described herein. Appropriate therapeutically effective concentrations and dosages can be readily determined by one skilled in the art.

Administration of the salts of the invention in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration of agents for serving similar utilities. The pharmaceutical compositions of the invention can be prepared by combining a

salt of the invention with an appropriate pharmaceutically acceptable excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. The pharmaceutical compositions of the invention can be prepared by combining a salt of the invention with an appropriate pharmaceutically acceptable excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as solid dispersions and solid solutions. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, buccal, rectal, vaginal, and intranasal. In a specific embodiment, the pharmaceutical composition is a tablet. Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a salt of the invention in aerosol form may hold a plurality of dosage units. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington: The Science and Practice of Pharmacy, 20th Edition (Philadelphia College of Pharmacy and Science, 2000). The composition to be administered will, in any event, contain a therapeutically effective amount of a salt of the invention for treatment of a disease or condition of interest in accordance with the teachings of this invention.

The pharmaceutical compositions of the invention may be prepared by methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be administered by injection can be prepared by combining a salt of the invention with sterile, distilled water so as to form a solution. A surfactant or other solubilizing excipient may be added to facilitate the formation of a homogeneous solution or suspension.

Surfactants are compounds that non-covalently interact with the salt of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

In other embodiments, a solid pharmaceutical composition intended for oral administration can be prepared by mixing a therapeutically effective amount of a salt of the invention with at least one suitable pharmaceutically acceptable excipient to form a solid pre-formulation composition, which then may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. Accordingly, in some embodiments, a pharmaceutical composition is provided, which includes a therapeutically effective amount of a salt of Formula (I) and a pharmaceutically acceptable excipient.

The salts of the invention are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy.

In some embodiments, the salts of the invention can be administered alone or in combination with other agents one time a day, or two times a day, or three times a day, or four times a day, for as long as the patient is infected, latently infected, or to prevent infection (e.g. for multiple years, months, weeks, or days).

In other embodiments, the compositions described herein may comprise substantially pure crystalline forms or may be substantially free of other crystalline forms and/or impurities.

In some embodiments, the composition comprises a crystalline form of Formula (I). In certain embodiments are provided compositions comprising a crystalline form as described herein, wherein the Formula (I) within the composition is substantially pure. In particular embodiments of compositions comprising a crystalline form of Formula (I), at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of Formula (I) present in the composition is one of the crystalline forms disclosed herein. In certain embodiments, the composition includes at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of one of the crystalline forms of Formula (I).

In other embodiments of compositions comprising a crystalline form disclosed herein, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of Formula (I) present in the composition are other amorphous or crystal forms of Formula (I) and/or impurities.

In yet other embodiments of compositions comprising the crystalline forms disclosed herein, impurities make up less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of the total mass relative to the mass of the crystalline forms present. Impurities may, for example, include by-products from synthesizing Formula (I), contaminants, degradation products, other crystalline forms, amorphous form, water, and solvents. In certain embodiments, impurities include by-products from the process of synthesizing Formula (I). In certain embodiments, impurities include contaminants from the process of synthesizing Formula (I). In certain embodiments, impurities include degradation products of Formula (I). In certain embodiments, impurities include other crystalline forms of Formula (I). In certain embodiments, impurities include other crystalline forms of Formula (I) and/or amorphous forms of Formula (I). In certain embodiments, impurities include water or solvent. In certain embodiments of compositions comprising a crystalline form disclosed herein, impurities are selected from the group consisting of by-products from synthesizing Formula (I), contaminants, degradation products, other crystalline forms, amorphous forms, water, solvents and combinations thereof.

Combination Therapy

In certain embodiments, a salt of a compound of Formula (I) disclosed herein, or a pharmaceutically acceptable salt thereof is used in a method for treating or preventing a respiratory condition or disease, for example, asthma, chronic obstructive pulmonary disease (COPD) or Cystic Fibrosis (CF), further comprising administering of the salt of the compound, in combination with one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents. Examples of additional therapeutic agents include compounds useful in the treatment of asthma, compounds useful in the treatment of COPD and/or compounds useful in the treatment of cystic fibrosis.

For example, compounds useful in the treatment of asthma include Inhaled corticosteroids (for example fluticasone (Flonase, Flovent HFA), budesonide (Pulmicort Flexhaler, Rhinocort), flunisolide (Aerospan HFA), ciclesonide (Alvesco, Omnaris, Zetonna), beclomethasone (Qnasl, Qvar), mometasone (Asmanex) or fluticasone furoate (Arnuity Ellipta)), Leukotriene modifiers(for example montelukast (Singulair), zafirlukast (Accolate) or zileuton (Zyflo); Long-acting beta agonists (for example salmeterol (Serevent) or formoterol (Foradil, Perforomist); Combination inhalers (for example fluticasone-salmeterol (Advair Diskus / Seretide), budesonide-formoterol (Symbicort) or formoterol-mometasone (Dulera) containing a long-acting beta agonist along with a corticosteroid); Theophylline (for example Theo-24 or Elixophyllin), Short-acting beta agonists (for example albuterol (ProAir HFA, Ventolin HFA, others) and levalbuterol (Xopenex)), Ipratropium (Atrovent) or oral or intravenous corticosteroids (for example prednisone or methylprednisolone)

For example, compounds useful in the treatment of COPD include short-acting bronchodilators (for example albuterol (ProAir HFA, Ventolin HFA, others), levalbuterol (Xopenex), and ipratropium (Atrovent)), long-acting bronchodilators (including tiotropium (Spiriva), salmeterol (Serevent), formoterol (Foradil, Perforomist), arformoterol (Brovana), indacaterol (Arcapta) and aclidinium (Tudorza)), Inhaled steroids (including Fluticasone (Flovent) and budesonide (Pulmicort), Combination inhalers (for example combining bronchodilators and inhaled steroids, for example Salmeterol and fluticasone (Advair) and formoterol and budesonide (Symbicort)), Oral steroids, Phosphodiesterase-4 inhibitors (for example roflumilast (Daliresp)) Theophylline and Antibiotics.

For example, compounds useful in the treatment of CF include Antibiotics, Mucus-thinning drugs, Bronchodilators and Oral pancreatic enzymes.

If the salt of the invention is to be used for the treatment of a condition associated with inflammation that benefits from enhancement or restoration of epithelial barrier function, then the further active agent is selected from the agents suitable for the condition in question.

In certain embodiments, the present disclosure provides a method for treating a respiratory disease, comprising administering to a subject in need thereof a therapeutically effective amount of a salt disclosed herein, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating a respiratory disease.

In certain embodiments, a salt disclosed herein, is administered with one or more additional therapeutic agents. Coadministration of a salt disclosed herein, with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a salt disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of the salt disclosed herein, and the one or more additional therapeutic agents are both present in the body of the subject. When administered sequentially, the combination may be administered in two or more administrations.

Co-administration includes administration of unit dosages of the salts disclosed herein, before or after administration of unit dosages of one or more additional therapeutic agents. For example, the salt disclosed herein, may be administered within seconds, minutes, or hours of the administration of the one or more additional therapeutic agents. In some embodiments, a unit dose of a salt disclosed herein, is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a salt disclosed herein within seconds or minutes. In other embodiments, a unit dose of a salt disclosed herein is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In yet other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a salt disclosed herein.

In certain embodiments, a salt disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a subject. In certain embodiments, such a unitary dosage form can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the salts disclosed can be dosed parenterally. In certain embodiments, the unitary dosage form can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the unitary dosage form is orally bioavailable and can be dosed orally. In certain embodiments, the unitary dosage form can be a solid dosage form for oral administration.

In certain embodiments, a salt disclosed herein, is formulated as a tablet, which may optionally contain one or more other compounds useful for treating a respiratory disease. In certain embodiments, the tablet can one or more other compounds useful for a respiratory disease, such as compounds useful in the treatment of asthma, compounds useful in the treatment of COPD and compounds useful in the treatment of cystic fibrosis, as described above. In certain embodiments, such tablets are suitable for once daily dosing.

It will be appreciated by one of skill in the art that the additional therapeutic agents listed above may be included in more than one of the classes listed above. The particular classes are not intended to limit the functionality of those compounds listed in those classes.

In certain embodiments, the crystalline forms are characterized by the interlattice plane intervals determined by an X-ray powder diffraction pattern (XRPD). The diffractogram of XRPD is typically represented by a diagram plotting the intensity of the peaks versus the location of the peaks, i.e., diffraction angle 2Θ (two-theta) in degrees. The characteristic peaks of a given XRPD can be selected according to the peak locations and their relative intensity to conveniently distinguish this crystalline structure from others.

Those skilled in the art recognize that the measurements of the XRPD peak locations and/or intensity for a given crystalline form of the same compound will vary within a margin of error. The values of degree 2Θ allow appropriate error margins. Typically, the error margins are represented by "±". For example, the degree 2Θ of about "8.7±0.3" denotes a range from about 8.7+0.3, i.e., about 9.0, to about 8.7-0.3, i.e., about 8.4. Depending on the sample preparation techniques, the calibration techniques applied to the instruments, human operational variation, and etc., those skilled in the art recognize that the appropriate error of margins for a XRPD can be ±0.5; ±0.4; ±0.3; ±0.2; ±0.1 ; ±0.05; or less. In certain embodiments of the invention, the XRPD margin of error is ±0.2. In certain embodiments of the invention, the XRPD margin of error is ±0.5.

In a further embodiment, there is provided is a method of producing a composition comprising one or more crystalline forms of Formula (I), wherein the method comprises combining a compound of Formula (I) with a suitable solvent or a mixture of suitable solvents to produce a composition comprising one or more crystalline forms of the compound of Formula (I). In a further embodiment, there is provided is another method of producing a composition comprising one or more crystalline forms of Formula (I), wherein the method comprises combining Formula (I) with a suitable solvent or a mixture of suitable solvents.

The choice of a particular solvent or combination of solvents or method of combining solvents affects the formation favouring one crystalline form of Formula (I) over another.

Solvents suitable for crystal formation include, for example: acetone, acetonitrile, ethyl acetate, heptane, isopropyl alcohol, methyl tert-butyl ether, toluene, water, and any mixtures thereof, for example, mixtures of isopropyl alcohol and heptane and ethylacetate.

Solvents suitable for crystal formation of the tartrate salt include, for example: methyl tert-butyl ether, acetone and isopropyl alcohol, and mixtures of isopropyl alcohol and water, and mixtures of heptane with ethylacetate.

Solvents suitable for crystal formation of the oxalate salt include, for example: methyl tert-butyl ether and ethyl acetate.

Solvents suitable for crystal formation of the naphthalenedisulfonate salt include, for example, acetone, methanol and methyl ethyl ketone (MEK).

The presence of impurities may affect the formation favouring one crystalline form of Formula (I) over another. In some embodiments, the form is prepared by a process comprising a compound of Formula (I) having impurities. In a further embodiment, the form is prepared by a process comprising substantially pure Formula (I).

In a further embodiment, provided is also one or more crystalline forms of Formula (I) produced according to any of the methods described herein.

It should be understood that the methods for preparing the crystalline forms described herein may yield quantity and quality differences compared to the methods for preparing a salt of Formula (I) produced on laboratory scale.

Tartrate

In a further embodiment, there is provided is a method of producing a composition comprising an tartrate salt of a compound of Formula (I), wherein the method comprises combining a compound of Formula (I) with a solvent to produce a composition comprising crystalline tartrate, wherein the solvent is isopropyl alcohol and water, for example, a mixture of isopropyl alcohol and water in a ratio from 90 to about 10 to about 99 to 1, for example 95 to about 5, or about 99 to 1.

In a further embodiment there is provided is the crystalline tartrate produced by combining a compound of Formula (I) with a solvent, wherein the solvent is isopropyl alcohol and water, for example, a mixture of isopropyl alcohol and water in a ratio from 90 to about 10 to about 99 to 1, for example about 95 to 5, or about 99 to 1.

Oxalate

In a further embodiment, there is provided is a method of producing a composition comprising a crystalline oxalate, wherein the method comprises combining Formula (I) with a solvent to produce a composition comprising the crystalline oxalate of a compound of Formula (I), wherein the solvent is methyl tert-butyl ether (MTBE).

In a further embodiment, there is provided is the crystalline oxalate produced by combining a compound of Formula (I) with a solvent, wherein the solvent is methyl tert-butyl ether.

Naphthalenedisulfonate

In a further embodiment, provided is a method of producing a composition comprising a crystalline naphthalenedisulfonate of a compound of Formula (I), wherein the method comprises combining a compound of Formula (I) with a solvent to produce a composition comprising the crystalline naphthalenedisulfonate of a compound of Formula (I), wherein the solvent is acetone.

In a further embodiment, there is provided is the crystalline naphthalenedisulfonate produced by combining Formula (I) with a solvent, wherein the solvent is acetone.

Hydrates

In a further embodiment, there is provided is a method of producing a composition comprising a crystalline compound of Formula (I) hydrate, wherein the method comprises combining a compound of Formula (I) with a stoichiometric or non-stoichiometric amount of solvent to produce a composition comprising crystalline compound of Formula (I) solvate, wherein the solvent is water. A compound of Formula (I), hydrate can have a range of water content depending on drying or hydrating conditions. In some embodiments, compound of Formula (I), hydrate has about 1, 2 or 3 equiv. of water.

Provided is crystalline compound of Formula (I) hydrate produced by combining Formula (I) with a solvent, wherein the solvent comprises water.

Uses in the treatment of disease

The crystalline forms and compositions thereof according to the invention are useful as medicaments for the treatment of respiratory diseases. In a further embodiment, the crystalline forms and compositions thereof according to the invention are useful as medicaments for the treatment of inborn, chronic, persistent or prolonged airway diseases. For example, they are effective in the treatment of conditions including asthma, chronic obstructive pulmonary disease (COPD), Cystic Fibrosis (CF), non-CF Bronchiectasis, chronic rhinosinusitis, diffuse panbronchiolitis (DPB), chronic bronchitis, Bronchiolitis Obliterans Organizing Pneumonia (BOOP) primary or secondary to chemotherapy or post-transplantation status, infantile respiratory distress syndrome (IRDS) and its long term complication, bronchopulmonary dysplasia, neuromuscular respiratory depression and/or failure, pneumonia (particularly community-acquired pneumonia) and conditions caused by and associated with Respiratory Syncytial Virus (RSV) and related viruses, for example the Human-Meta-Pneumo Virus, such as chronic infantile wheezing and associated childhood asthma bronchial hyperreactivity. In one embodiment, the crystalline forms and compositions thereof according to the invention are useful as medicaments for the treatment of asthma, chronic obstructive pulmonary disease (COPD) or Cystic Fibrosis (CF).

Uses in Manufacturing of Drug Product

According to a further embodiment, there is provided is a use of the crystalline forms described herein in the manufacture of a drug product. The one or more of the crystalline forms described herein may be used in the manufacturing process to produce the drug product. The one or more of the crystalline forms described herein may be used as an intermediate in the manufacturing process to produce the drug product.

In certain embodiments, crystalline salts of Formula (I) are used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, the tartrate of a compound of Formula (I) is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, the oxalate of a compound of Formula (I) is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, the naphthalene disulfonate salt of a compound of Formula (I) is used in the manufacture of an active pharmaceutical ingredient.

Articles of Manufacture and Kits

Compositions comprising one or more of the crystalline forms described hereinand formulated in one or more pharmaceutically acceptable excipients or other ingredients can be prepared, placed in an appropriate container, and labelled for treatment of an indicated condition. Accordingly, there also is contemplated an article of manufacture, such as a container comprising a dosage form of one or more of the crystalline forms described herein and a label containing instructions for use of the compound^

In some embodiments, the article of manufacture is a container comprising a dosage form of one or more of the crystalline forms described herein, and one or more pharmaceutically acceptable excipients or other ingredients. In some embodiments of the articles of manufacture described herein, the dosage form is a solution.

Kits also are contemplated. For example, a kit can comprise a dosage form of a pharmaceutical composition and a package insert containing instructions for use of the composition in treatment of a medical condition. In a further embodiment a kit may comprise multiple individual dosage forms, each comprising a therapeutically effective amount of a salt as described herein, and instructions for their administration to a human in need thereof. Each of the individual dosage forms may comprise a therapeutically effective amount of a salt as described herein in combination with at least one pharmaceutically effective excipient. The individual dosage forms may be in the form of, as examples, a solution, a tablet, a pill, a capsule, a sachet, a sublingual medicament, a lyophilized powder, a spray-dried powder, or a liquid composition for oral, parenteral, or topical administration. The instructions for use in the kit may be for treating a respiratory disease. The instructions may be directed to any of the respiratory diseases and methods described herein. The instructions may be for prophylaxis or the treatment of an existing respiratory disease.

In certain embodiments, the crystalline or salt forms described herein may potentially exhibit improved properties. For example, in certain embodiments, the crystalline or salt forms described herein may potentially exhibit improved stability. Such improved stability could have a potentially beneficial impact on the manufacture of the compound of Formula (I), such as for example offering the ability to store process intermediate for extended periods of time. Improved stability could also potentially benefit a composition or pharmaceutical composition of the compound of Formula (I). In certain embodiments, the crystalline or salt described herein may also potentially result in improved

yield of the compound of Formula (I), or potentially result in an improvement of the quality of the compound of Formula (I). In certain embodiments, the crystalline, salt and solvate forms described herein may also exhibit improved pharmacokinetic properties and/or potentially improved bioavailability.

Definitions

Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is as "including, but not limited to".

Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment.

Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

Embodiments that reference throughout this specification to "a compound" includes the crystalline, salt, co-crystal, and solvate forms of the formulas and/or compounds disclosed herein.

The term 'about' refers to a tolerance of ±20% of the relevant value, for example ±15% of the relevant value, such as ±10% of the relevant value or ±5% of the relevant value.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Pharmaceutically acceptable excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavour enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, and/or emulsifier, or a combination of one or more of the above which has been approved by the United States Food and Drug Administration, or equivalent national drug regulatory body, as being acceptable for use in humans or domestic animals.

A "pharmaceutical composition" refers to a formulation of a salt of the invention and a medium generally accepted in the art for the delivery of the biologically active salt to mammals, e.g. , humans. Such a medium includes all pharmaceutically acceptable excipients therefor.

"Effective amount" or "therapeutically effective amount" refers to an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or clinician. The amount of a compound according to the invention

which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

The term 'hemi salt' refers to a salt wherein then the stoichiometry is one atom of the counter ion to two atoms of the compound of Formula (I).

The term 'mono salt' refers to a salt wherein then the stoichiometry is one atom of the counter ion to one atom of the compound of Formula (I).

The term 'bis salt' refers to a salt wherein then the stoichiometry is two atoms of the counter ion to one atoms of the compound of Formula (I).

The terms "subject" or "patient" refer to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal (or the patient). In some embodiments the subject (or the patient) is human, domestic animals (e.g., dogs and cats), farm animals (e.g., cattle, horses, sheep, goats and pigs), and/or laboratory animals (e.g., mice, rats, hamsters, guinea pigs, pigs, rabbits, dogs, and monkeys). In some embodiments, the subject (or the patient) is a human. "Human (or patient) in need thereof refers to a human who may have or is suspect to have diseases or conditions that would benefit from certain treatment; for example, being treated with the compounds disclosed herein according to the present application.

"Unit dosage forms" are physically discrete units suitable as unitary dosages for subjects (e.g. , human subjects and other mammals), each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The term "substantially as shown in" when referring, for example, to an XRPD pattern, a DSC thermal profile, a DVS graph, or a TGA thermal profile includes a pattern, thermal profile or graph that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art.

In some embodiments, the term "substantially pure" or "substantially free" with respect to a particular crystalline form of a compound means that the composition comprising the crystalline form contains less than 99%, less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, or less than 1 % by weight of other

substances, including other crystalline forms and/or impurities. In certain embodiments, "substantially pure" or "substantially free of refers to a substance free of other substances, including other crystalline forms and/or impurities. Impurities may, for example, include by-products or left over reagents from chemical reactions, contaminants, degradation products, other crystalline forms, water, and solvents.

Each of the references including all patents, patent applications and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application. Each of the references including all patents, patent applications and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.

Description of the figures

Figure 1: X-Ray powder diffractogram for the tartrate of a compound of Formula (I).

Figure 2: X-Ray powder diffractogram for the oxalate of a compound of Formula (I).

Figure 3: X-Ray powder diffractogram for the naphthalene-1,5-disulfonate of a compound of Formula (I).

Figure 4a: Thermogravimetric analysis (TGA) (Black line) and Differential scanning calorimetry (Red Line) thermal profiles for the dihydrate tartrate salt of a compound of Formula (I).

Figure 4b: Thermogravimetric analysis (TGA) (Black line) and Differential scanning calorimetry (Red Line) thermal profiles for the trihydrate tartrate salt of a compound of Formula (I).

Figure 4c: Thermogravimetric analysis (TGA) (Red Line) and Differential scanning calorimetry (Black Line) thermal profiles for the tartrate salt of a compound of Formula (I).

Figure 4d: Thermogravimetric analysis (TGA) (Red Line) and Differential scanning calorimetry (Black Line) thermal profiles for the tartrate salt of a compound of Formula (I).

Figure 5a: Dynamic Vapor Sorption (DVS) profile of the tartrate compound of Formula (I).

Figure 5b: Dynamic Vapor Sorption (DVS) profile of the tartrate compound of Formula (I).

Figure 6a. Proton NMR of the tartrate of a compound of Formula (I) – 1:1 salt

Figure 6b. Proton NMR of the tartrate of a compound of Formula (I) – bis tartrate.

Figure 7. Proton NMR of the oxalate of a compound of Formula (I).

Figure 8. Proton NMR of the naphthalene-1,5-disulfonate of a compound of Formula (I).

The invention is now illustrated by the following non-limiting examples, using the following methodologies.

X-Ray Powder Diffraction (XRPD) (Tartrate)

X-Ray Powder Diffraction patterns were collected on a PANalytical diffractometer using Cu Kα radiation (45kV, 40mA), θ - θ goniometer, focusing mirror, divergence slit (1/2''), soller slits at both incident and divergent beam (4mm) and a PIXcel detector. 13 The software used for data collection was X'Pert Data Collector, version 2.2f and the data was presented using X'Pert Data Viewer, version 1.2d. XRPD patterns were acquired under ambient conditions via a transmission foil sample stage (polyimide - Kapton, 12.7μm thickness film) under ambient conditions using a PANalytical X'Pert PRO. The data collection range was 2.994 - 35°2θ with a continuous scan speed of 0.202004°s^{-1} .

X-Ray Powder Diffraction (XRPD) (oxalate)

The X-ray powder diffraction pattern is measured on a PanAlytical X'Pert Pro powder diffractometer working in Bragg-Brentano geometry with Cu K alpha radiation.

Power: 45 kV / 40 mA

Monocromator: Johansson (1.540598 Å)

Detector: Pixcel

2-Theta range: 2 – 35°

Scan speed: 0.03 °/s

Step size: 0.013°

Sample rotation: 7.5 rpm

The X-ray powder diffraction pattern peaks are expressed in terms of the 2 theta ± 0.2 (degrees).

X-Ray Powder Diffraction (XRPD) (naphthalene-1,5-disulfonate)

The X-ray powder diffraction pattern was measured on a Bruker D8 Discover powder diffractometer working in Bragg-Brentano geometry with Cu K alpha radiation, using the following settings:

Power: 40 kV / 40 mA

Monocromator: No

Detector: LYNXEYE XE-T

2-Theta range: 5 – 60°

Time per step: 1.4 s

Step size [°2theta]: 0.02

Sample rotation: No

The X-ray powder diffraction pattern peaks are expressed in terms of the 2 theta ± 0.2 (degrees).

Thermo-Gravimetric Analysis (TGA)

TGA data were collected on a PerkinElmer Pyris 1 TGA equipped with a 20-position auto-sampler. The instrument was calibrated using a certified weight and certified Alumel and Perkalloy for temperature. A predefined amount of the sample, 1-5mg, was loaded onto a pre-tared aluminium crucible and was heated at 20ºC.min-1 from ambient temperature to 400ºC. A nitrogen purge at 20ml.min-1 was maintained over the sample. Instrument control, data acquisition and analysis was performed with Pyris Software v11.1.1 revision H.

Differential Scanning Calorimetry

DSC data was collected on a PerkinElmer Pyris 6000 DSC equipped with a 45-position sample holder. The instrument was verified for energy and temperature calibration using certified indium. A predefined amount of the sample, 0.5-3.0mg, was placed in a pin holed aluminium pan and heated at 20ºC.min-1 from 30 to 350ºC, or varied as experimentation dictated. A purge of dry nitrogen at 20ml min-1 was maintained over the sample. The instrument control, data acquisition and analysis was performed with Pyris Software v11.1.1 revision H.

Hot Stage Microscopy (HSM)

Hot Stage Microscopy was undertaken using a Leica DME polarised light microscope combined with a Mettler-Toledo MTFP82HT hot-stage and a digital video camera for image capture. A small amount of each sample was placed onto a glass slide with individual particles separated as best as possible. The sample was viewed with appropriate magnification and partially polarised light, whilst being heated from ambient temperature typically at 20°C.min^{-1} unless an alternate heating rate is stated.

Dynamic Vapour Sorption

Sorption isotherms were obtained using a Hiden Isochema moisture sorption analyser (model IGAsorp), controlled by IGAsorp Systems Software V6.50.48. The sample was maintained at a constant temperature (25ºC) by the instrument controls. The humidity was controlled by mixing streams of dry and wet nitrogen, with a total flow of 250ml.min^{-1}. The instrument was verified for relative humidity content by measuring three calibrated Rotronic salt solutions (10 - 50 - 88%). The weight change of the sample was monitored as a function of humidity by a microbalance (accuracy +/- 0.005 mg). A defined amount of sample was placed in a tared mesh stainless steel basket under ambient conditions. A full experimental cycle typically consisted of three scans (sorption, desorption and sorption) at a constant temperature (25ºC) and 10% RH intervals over a 0 – 90% range (60 minutes for each humidity level). This type of experiment should demonstrate the ability of samples studied to absorb moisture (or not) over a set of well-determined humidity ranges.

Solution Proton NMR

^{1}H NMR spectra were collected using a JEOL ECX 400MHz spectrometer equipped with an auto-sampler. The samples were dissolved in a suitable deuterated solvent for analysis. The data was acquired using Delta NMR Processing and Control Software version 4.3 (Joel, Massachusetts, USA).

The proton NMR spectra for the tartrate and naphthalenedisulfonate are shown in Figures 6 (a and b) and 8 respectively and provide information on the ratio of salt to the compound of Formula (1). Figure 7 show the proton NMR spectra for the oxalate, although the oxalate cannot be detected in the spectra and therefore, no such assessment was possible for the oxalate used proton NMR under the conditions used.

Single crystal X-ray diffraction

The compound of Formula (I) naphthalene-1,5-disulfonate was recrystallized from methanol / ethylmethylketone.

The single crystal X-ray measurement showed the following:

Lattice type: P

Space group: P 21 21 21

Example 1: Preparation of : (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate

The compound of Formula (I) free base (50mg) was dissolved in 0.5ml of isopropyl alcohol/water (95:5) and was stirred at 25°C for 30 minutes. 1 equivalent of tartaric acid was added as a 0.5M solution in tetrahydrofuran and the mixture stirred at 25°C for 20 hours. The resulting suspension was filtered to recover the tartrate salt of [[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) tartrate. The solid recovered was dried *in vacuo* for 20 hours, prior to characterisation.

Example 2: Preparation of : (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) oxalate

The compound of Formula (I) (50 mg, 1 eq) was dissolved in MTBE (0.5 mL) and stirred for 10 minutes. Oxalic acid (18 mg, 4 eq) dissolved in methyl tert-butyl ether (MTBE) (0.2 mL) was added dropwise. The mixture was stirred at 35-40°C overnight and then, at room temperature for 4 days. The precipitate was filtered to obtain (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate)oxalate as a white powder.

Example 3: Preparation of : (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate) naphthalenedisulfonate

The compound of Formula (I) (50 mg, 1 eq) was dissolved in acetone (0.7 mL) and the mixture was stirred for 15 minutes on ice. Naphthalene-1,5-disulfonic acid (26 mg, 1 eq) was dissolved in acetone (0.3 mL). The acid solution was added dropwise to the cooled solution of the compound of Formula (I). The mixture was stirred on ice for 10-15 minutes and filtered to obtain (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate)naphthalene-1,5-disulfonate as a white powder.

Claims

1. A crystalline salt form of the compound (2S,3R,4S,6R)-4-(dimethylamino)-2-[[(2R,3S,4R,5R,8R,10R,11R,12S,13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-1-oxa-6-azacyclopentadec-11-yl]oxy]-6-methyl-tetrahydropyran-3-yl] benzoate).

2. A crystalline salt form of the compound of Claim 1 wherein the salt is the tartrate.

3. A crystalline salt form of the compound of Claim 1 wherein the salt is the oxalate.

4. A crystalline salt form of the compound of Claim 1 wherein the salt is the naphthalene disulfonate, such as the naphthalene 1,5-disulfonate.

5. A crystalline salt form of the compound of any one of claims 1 to 4 wherein the salt is a hemi, mono or bis salt.

6. A crystalline salt form of the compound of any one of claims 1 to 5 wherein the salt is a hydrate, for example, a channel hydrate.

7. A crystalline tartrate salt form of Claim 2 characterised by one or more peaks on a 2-theta scale in an XRPD spectrum selected from the group comprising 5.3°, 6.5°, 8.4°, 9.3°, 10.8°, 14.3°, 15.9°, 17.2°, 18.8° and 21.9°θ ± 0.2° 2θ.

8. A crystalline tartrate salt form of Claim 2 characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 5.3°, 6.5° and 8.4° 2θ ± 0.2° 2θ.

9. A crystalline tartrate salt form of Claim 8 characterized by an X-ray powder diffraction (XRPD) pattern further comprising peaks at 10.8°, and 17.2° 2θ ± 0.2° 2θ.

10. A crystalline tartrate salt form of Claim 8 or Claim 9 characterized by an X-ray powder diffraction (XRPD) pattern further comprising peaks at. 9.3°, 14.3° and 21.9° 2θ ± 0.2° 2θ

11. A crystalline tartrate salt form of Claim 2 characterized by an X-ray powder diffraction substantially as set forth in Figure 1.

12. A crystalline tartrate salt form of Claim 2 characterized by differential scanning calorimetry (DSC) pattern substantially as set forth in any one of Figure 4a, 4b, 4c or 4d.

13. A crystalline tartrate salt form of Claim 2, characterized by thermogravimetric analysis (TGA) pattern substantially as set forth in any one of Figure 4a, 4b, 4c or 4d.

14. A crystalline tartrate salt form of Claim 2, characterized by a dynamic vapor sorption (DVS) pattern substantially as set forth in Figure 5a or Figure 5b.

15. The crystalline oxalate salt form of Claim 3 characterised by one or more peaks on a 2-theta scale in an XRPD spectrum selected from the group comprising 9.2°, 11.9°, 15.8°, 16.1°, 16.3°, 16.4°, 17.7°, 18.5°, 18.7°, and 19.6° 2θ ± 0.2° 2θ .

16. The crystalline oxalate salt form of Claim 3 characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 9.2°, 16.1°, 16.3°, 18.7°, 19.6° 2θ ± 0.2° 2θ.

17. The crystalline oxalate salt form of Claim 16 characterized by an X-ray powder diffraction (XRPD) pattern further comprising peaks at 11.9°, 15.8°, 16.4°, 17.7°, 18.5° 2θ ± 0.2° 2θ.

18. The crystalline oxalate salt form of Claim 3 characterized by an X-ray powder diffraction substantially as set forth in Figure 2.

19. The crystalline naphthalenedisulphonate salt form of Claim 4 characterised by one or more peaks on a 2-theta scale in an XRPD spectrum selected from the group comprising 5.6°, 8.9°, 10.0°, 10.5°, 11.4°, 12.7°, 13.5°, 16.3°, 18.1° and 20.3 ° 2θ ± 0.2° 2θ.

20. The crystalline naphthalenedisulphonate salt form of Claim 4 characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 8.9°, 10.0°, 10.5°, 12.7° and 18.1° 2θ ± 0.2° 2θ.

21. The crystalline naphthalenedisulphonate salt form of Claim 20 characterized by an X-ray powder diffraction (XRPD) pattern further comprising peaks at 5.6°, 11.4°, 13.5°, 16.3°, 20.3° 2θ ± 0.2° 2θ.

22. The crystalline naphthalenedisulphonate salt form of Claim 4 characterized by an X-ray powder diffraction substantially as set forth in Figure 3.

23. A pharmaceutical composition comprising a therapeutically effective amount of a crystalline salt form as defined in any one of the preceding claims and a pharmaceutically acceptable excipient.

24. A crystalline salt form, as defined in any one of claims 1 to 22 or a pharmaceutical composition as claimed in claim 23 for use in treating a respiratory disease.

25. A crystalline salt form, as defined in any one of claims 1 to 22 or a pharmaceutical composition as claimed in claim 23 for use in treating asthma, chronic obstructive pulmonary disease (COPD) or Cystic Fibrosis (CF).